



Clinical trial results:

A 12-month, phase IV, randomized, open label, multicenter study to compare efficacy of 0.5 mg ranibizumab PRN versus 2 mg aflibercept bimonthly intravitreal injections on retinal thickness stability till month 6 of treatment and explore functional outcomes up to month 12 in patients with neovascular (wet) age-related macular degeneration (AMD)

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2013-002431-15 |
| Trial protocol | DE SE NO AT DK BE NL PT |
| Global end of trial date | 29 May 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 02 June 2018 |
| First version publication date | 02 June 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CRFB002ADE23 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01958918 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | Sint Johan Campus, Basel, Switzerland, 4002 |
| Public contact | Study Director, Novartis, novartis.email@novartis.com |
| Scientific contact | Study Director, Novartis Pharma AG, +41 613241111, Novartis.email@novartis.com |

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 | 29 May 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 May 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 May 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare the treatment effect of ranibizumab pro re nata (PRN) (BCVA loss and/or SD-OCT disease activity guided retreatment) versus aflibercept bimonthly regimen on central subfield retinal thickness (CSRT) stability as measured by mean CSRT fluctuations between Month 3 and Month 6.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International conference of 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 | 23 October 2013 |
| 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: 57 |
| Country: Number of subjects enrolled | Belgium: 7 |
| Country: Number of subjects enrolled | Denmark: 27 |
| Country: Number of subjects enrolled | France: 51 |
| Country: Number of subjects enrolled | Germany: 412 |
| Country: Number of subjects enrolled | Netherlands: 16 |
| Country: Number of subjects enrolled | Norway: 7 |
| Country: Number of subjects enrolled | Portugal: 108 |
| Country: Number of subjects enrolled | Sweden: 6 |
| Country: Number of subjects enrolled | Switzerland: 16 |
| Worldwide total number of subjects | 707 |
| EEA total number of subjects | 634 |

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) | 35 |
| From 65 to 84 years | 536 |
| 85 years and over | 136 |

Subject disposition

Recruitment

Recruitment details:

A total of 712 patients were treated, but only 707 patients had a post baseline assessment. Therefore the full analysis set consists of 707 patients. The safety set includes the 712 treated patients.

Pre-assignment

Screening details:

This reporting group included all patients randomized to one of the treatment arms (Randomized Set)

The Full Analysis Set (FAS) consisted of all patients who received at least one application of study treatment and had at least one post-baseline assessment for SD-OCT.

Period 1

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

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ranibizumab |

Arm description:

0.5 mg intravitreal injections of ranibizumab monthly until maximum stable BCVA with retreatment based on BCVA loss and/or SD-OCT signs of wet AMD disease activity.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Lucentis |
| Investigational medicinal product code | RFB002 |
| Other name | Lucentis |
| Pharmaceutical forms | Blood fraction modifier, Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

0.5 mg intravitreal injections monthly

| | |
|------------------|-------------|
| Arm title | Aflibercept |
|------------------|-------------|

Arm description:

2 mg intravitreal injections of aflibercept monthly for the first 3 months, followed by 2 mg intravitreal injections once every 2 months (current EU SmPC label)

| | |
|--|------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Aflibercept |
| Investigational medicinal product code | NA |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

2 mg intravitreal injections monthly

| Number of subjects in period 1 | Ranibizumab | Aflibercept |
|---------------------------------------|-------------|-------------|
| Started | 353 | 354 |
| Full analysis set | 353 | 354 |
| Completed | 313 | 314 |
| Not completed | 40 | 40 |
| Adverse event, serious fatal | 1 | 3 |
| Consent withdrawn by subject | 11 | 7 |
| Adverse event, non-fatal | 12 | 12 |
| administrative problems | - | 2 |
| Lost to follow-up | 3 | 6 |
| Lack of efficacy | 13 | 10 |

Baseline characteristics

Reporting groups

| | |
|--|-------------|
| Reporting group title | Ranibizumab |
| Reporting group description: 0.5 mg intravitreal injections of ranibizumab monthly until maximum stable BCVA with retreatment based on BCVA loss and/or SD-OCT signs of wet AMD disease activity. | |
| Reporting group title | Aflibercept |
| Reporting group description: 2 mg intravitreal injections of aflibercept monthly for the first 3 months, followed by 2 mg intravitreal injections once every 2 months (current EU SmPC label) | |

| Reporting group values | Ranibizumab | Aflibercept | Total |
|--|-------------|-------------|-------|
| Number of subjects | 353 | 354 | 707 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 18 | 17 | 35 |
| From 65-84 years | 267 | 269 | 536 |
| 85 years and over | 68 | 68 | 136 |
| Age Continuous Units: years | | | |
| arithmetic mean | 77.3 | 78.0 | - |
| standard deviation | ± 7.53 | ± 7.21 | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 210 | 218 | 428 |
| Male | 143 | 136 | 279 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Caucasian | 350 | 352 | 702 |
| Asian | 1 | 0 | 1 |
| Other | 2 | 2 | 4 |

Subject analysis sets

| | |
|--|-------------------|
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients randomized (treated) with post baseline assessment | |

| | | | |
|---|-------------------|--|--|
| Reporting group values | Full analysis set | | |
| Number of subjects | 707 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 35 | | |
| From 65-84 years | 536 | | |
| 85 years and over | 136 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 77.7 | | |
| standard deviation | ± 7.38 | | |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 428 | | |
| Male | 279 | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Caucasian | 702 | | |
| Asian | 1 | | |
| Other | 4 | | |

End points

End points reporting groups

| | |
|--|-------------------|
| Reporting group title | Ranibizumab |
| Reporting group description: 0.5 mg intravitreal injections of ranibizumab monthly until maximum stable BCVA with retreatment based on BCVA loss and/or SD-OCT signs of wet AMD disease activity. | |
| Reporting group title | Aflibercept |
| Reporting group description: 2 mg intravitreal injections of aflibercept monthly for the first 3 months, followed by 2 mg intravitreal injections once every 2 months (current EU SmPC label) | |
| Subject analysis set title | Full analysis set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients randomized (treated) with post baseline assessment | |

Primary: Mean of the absolute values of CSRT difference Month 3 to Month 6

| | |
|--|---|
| End point title | Mean of the absolute values of CSRT difference Month 3 to Month 6 |
| End point description: The thickness of the retina was measured by Spectral Domain Optical Coherence Topography (SD-OCT). The mean of the absolute values of the CSRT difference between Month 3 and 4, Month 4 and 5, and Month 5 and 6 was calculated (ie, CSRT fluctuation). A lower average CSRT fluctuation demonstrates greater retinal stability. One eye (study eye) contributed to the analysis. | |
| End point type | Primary |
| End point timeframe: Month 3, Month 4, Month 5, Month 6 | |

| End point values | Ranibizumab | Aflibercept | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 345 | 340 | | |
| Units: micrometers | | | | |
| arithmetic mean (standard error) | 25.16 (\pm 2.584) | 29.28 (\pm 2.620) | | |

Statistical analyses

| | |
|---|---------------------------|
| Statistical analysis title | Comparison |
| Comparison groups | Ranibizumab v Aflibercept |
| Number of subjects included in analysis | 685 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.185 |
| Method | ANOVA |

Secondary: Total Best Corrected Visual Acuity (BCVA) Score at Month 12

| | |
|-----------------|---|
| End point title | Total Best Corrected Visual Acuity (BCVA) Score at Month 12 |
|-----------------|---|

End point description:

Visual acuity was assessed in a sitting position with refraction using ETDRS-like visual acuity testing charts at an initial testing distance of 4 meters. A higher score indicates better visual acuity. One eye (study eye) contributed to the analysis.

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

End point timeframe:

Month 12

| End point values | Ranibizumab | Aflibercept | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 313 | 312 | | |
| Units: letters | | | | |
| arithmetic mean (standard deviation) | 66.4 (± 18.10) | 68 (± 17.62) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: IREST at Month 12

| | |
|-----------------|-------------------|
| End point title | IREST at Month 12 |
|-----------------|-------------------|

End point description:

Number of incorrectly read words (IREST) was assessed using International Reading Speed Texts (IREsT) and measured in words per minute.

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

End point timeframe:

Month 12

| End point values | Ranibizumab | Aflibercept | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 253 | 251 | | |
| Units: incorrect words per minute | | | | |
| arithmetic mean (standard deviation) | 5.7 (± 21.19) | 6.1 (± 21.86) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: National Eye Institute Visual Functioning Questionnaire Composite Score (VFQ-25) at Month 12

| | |
|---|--|
| End point title | National Eye Institute Visual Functioning Questionnaire Composite Score (VFQ-25) at Month 12 |
| End point description: Vision-related quality of life was assessed by the patient using the National Eye Institute Visual Function Questionnaire. The scores of 12 subscales (general health, general vision, ocular pain, near activities, distance activities, social function, mental health, role difficulties, dependency, driving, color vision, and peripheral vision) were added together for a total (composite) score, which ranged from 0 to 100. A higher score indicates poorer function. | |
| End point type | Secondary |
| End point timeframe: Month 12 | |

| End point values | Ranibizumab | Aflibercept | | |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 305 | 297 | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 80.0 (± 14.43) | 79.1 (± 14.95) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Correlations between CSRT fluctuation (Month 3 to 6) and functional outcomes at Month 12 (Full Analysis Set)

| | |
|--|--|
| End point title | Correlations between CSRT fluctuation (Month 3 to 6) and functional outcomes at Month 12 (Full Analysis Set) |
| End point description: Correlation coefficient calculated based on Pearson's correlation between each corresponding parameter and CSRT stability. | |
| End point type | Secondary |
| End point timeframe: Month 3 to Month 6, Month 12 | |

| End point values | Ranibizumab | Aflibercept | | |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 353 | 354 | | |
| Units: correlation coefficient | | | | |
| number (not applicable) | | | | |
| Total BCVA Score | -0.2194 | 0.0155 | | |
| IREST reading speed (words/minute) | 0.0889 | 0.0847 | | |
| VFQ-25 composite score | 0.1064 | 0.0847 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

| | |
|-----------------|------------|
| 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 | Aflibercept 2 mg |
|-----------------------|------------------|

Reporting group description:

Aflibercept 2 mg

| Serious adverse events | Ranibizumab 0.5 mg | Aflibercept 2 mg | |
|---|--------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 67 / 356 (18.82%) | 74 / 356 (20.79%) | |
| number of deaths (all causes) | 1 | 3 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Anal cancer | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon adenoma | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal stromal tumour | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-small cell lung cancer | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Penile cancer | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cell carcinoma | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal neoplasm | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arteriosclerosis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 4 / 356 (1.12%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral arterial occlusive disease | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Medical device site joint pain | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Non-cardiac chest pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Atrophic vulvovaginitis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Emotional distress | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Body temperature decreased | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Acetabulum fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ankle fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Concussion | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Contusion | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 3 / 356 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laceration | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pubis fracture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 3 / 356 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sternal fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Hydrocele | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 5 / 356 (1.40%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congestive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 3 / 356 (0.84%) | 4 / 356 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 356 (0.56%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stress cardiomyopathy | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systolic dysfunction | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Akinesia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem stroke | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 3 / 356 (0.84%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebellar infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 356 (0.84%) | 3 / 356 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Cervical myelopathy | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Formication | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glossopharyngeal neuralgia | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkinesia | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lacunar infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular dementia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iron deficiency anaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 356 (0.28%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Sudden hearing loss | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Amaurosis fugax | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angle closure glaucoma | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Detachment of macular retinal | | | |

| | | | |
|---|-----------------|-----------------|--|
| pigment epithelium | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ectropion | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iridocyclitis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ocular hypertension | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal pigment epithelial tear | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ulcerative keratitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vitreous adhesions | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 3 / 356 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crohn's disease | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastritis | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal polyp | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal hypertensive gastropathy | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subileus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varices oesophageal | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct stone | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic cirrhosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Portal hypertension | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urethral dilatation | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Goitre | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 3 / 356 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 2 / 356 (0.56%) | 3 / 356 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 4 / 356 (1.12%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Spinal column stenosis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess oral | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endophthalmitis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 2 / 356 (0.56%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infectious pleural effusion | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lip infection | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver abscess | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 356 (0.28%) | 4 / 356 (1.12%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 0 / 356 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 3 / 356 (0.84%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid retention | | | |
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 356 (0.00%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 356 (0.28%) | 1 / 356 (0.28%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Ranibizumab 0.5 mg | Aflibercept 2 mg | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 156 / 356 (43.82%) | 156 / 356 (43.82%) | |
| Investigations | | | |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 29 / 356 (8.15%) | 23 / 356 (6.46%) | |
| occurrences (all) | 46 | 28 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 16 / 356 (4.49%) | 21 / 356 (5.90%) | |
| occurrences (all) | 21 | 28 | |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 41 / 356 (11.52%) | 28 / 356 (7.87%) | |
| occurrences (all) | 47 | 30 | |
| Dry eye | | | |
| subjects affected / exposed | 18 / 356 (5.06%) | 11 / 356 (3.09%) | |
| occurrences (all) | 19 | 12 | |
| Eye pain | | | |
| subjects affected / exposed | 24 / 356 (6.74%) | 23 / 356 (6.46%) | |
| occurrences (all) | 36 | 26 | |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 20 / 356 (5.62%) | 9 / 356 (2.53%) | |
| occurrences (all) | 22 | 12 | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 19 / 356 (5.34%) | 25 / 356 (7.02%) | |
| occurrences (all) | 21 | 41 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 12 / 356 (3.37%) 15 | 21 / 356 (5.90%) 23 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 22 / 356 (6.18%) | 12 / 356 (3.37%) | |
| occurrences (all) | 23 | 12 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 43 / 356 (12.08%) | 62 / 356 (17.42%) | |
| occurrences (all) | 54 | 82 | |

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