



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
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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
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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
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Arm title	Ranibizumab
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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
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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
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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
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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 (\pm 18.10)	68 (\pm 17.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: IREST at Month 12

End point title	IREST at Month 12
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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
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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 (\pm 21.19)	6.1 (\pm 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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.1
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Reporting groups

Reporting group title	Ranibizumab 0.5 mg
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Reporting group description:

Ranibizumab 0.5 mg

Reporting group title	Aflibercept 2 mg
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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 occurrences (all)	22 / 356 (6.18%) 23	12 / 356 (3.37%) 12	
Viral upper respiratory tract infection			
subjects affected / exposed occurrences (all)	43 / 356 (12.08%) 54	62 / 356 (17.42%) 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