Clinical trial results:
A Two-Year, Randomized, Double-Masked, Multicenter, Two-Arm Study Comparing the Efficacy and Safety of RTH258 6mg Versus Aflibercept in Subjects with Neovascular Age-Related Macular Degeneration

Summary

EudraCT number	2014-004886-26
Trial protocol	SK PT FI AT NO IE ES EE LT SE DE HU CZ NL GB LV DK BE PL GR HR IT
Global end of trial date	08 March 2018

Results information

Result version number	v1
This version publication date	16 March 2019
First version publication date	16 March 2019

Trial information

Trial identification

Sponsor protocol code	RTH258-C002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02434328
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alcon Research, Ltd.
Sponsor organisation address	6201 S. Freeway, Fort Worth, TX, United States, 76134
Public contact	EMEA Regulatory Affairs, Alcon Eye Care UK Ltd, eurmea.ra@alcon.com
Scientific contact	EMEA Regulatory Affairs, Alcon Eye Care UK Ltd, eurmea.ra@alcon.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	08 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to compare brolucizumab (RTH258) ophthalmic solution for intravitreal (IVT) injection (6 mg) to aflibercept ophthalmic solution for IVT injection (2 mg) in subjects with untreated active choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD) in the study eye.

Subjects were randomized to brolucizumab 6 mg and aflibercept 2 mg in a 1:1 ratio. Subjects in both treatment arms received 3 monthly loading doses (Day 0, Week 4 and Week 8), followed by a maintenance regimen, until the end of the study. All subjects attended pre-specified visits every 4 weeks.

Protection of trial subjects:

Prior to the start of the study, the study protocol, the informed consent and assent documents, patient instruction sheets, the Investigator’s Brochure, as well as any advertising materials used to recruit patients were submitted to institutional review boards (IRBs) and independent ethics committees (IECs). The IRB/IECs reviewed all documents and approved required documents; copies of the approval letters were provided to Alcon. Consistent with both the IRB/IEC’s requirements and all applicable regulations, the Investigators periodically provided study updates to the IRB/IEC. This study was conducted in accordance with Good Clinical Practices (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 July 2015
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	Netherlands: 9
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 60
Country: Number of subjects enrolled	Portugal: 15
Country: Number of subjects enrolled	Slovakia: 46
Country: Number of subjects enrolled	Spain: 114
Country: Number of subjects enrolled	United Kingdom: 35
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 2

Country: Number of subjects enrolled	Czech Republic: 38
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Estonia: 12
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 83
Country: Number of subjects enrolled	Germany: 31
Country: Number of subjects enrolled	Greece: 15
Country: Number of subjects enrolled	Hungary: 84
Country: Number of subjects enrolled	Ireland: 5
Country: Number of subjects enrolled	Italy: 42
Country: Number of subjects enrolled	Latvia: 12
Country: Number of subjects enrolled	Lithuania: 11
Country: Number of subjects enrolled	Switzerland: 17
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Turkey: 21
Country: Number of subjects enrolled	Vietnam: 9
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Korea, Republic of: 28
Worldwide total number of subjects	739
EEA total number of subjects	647

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)	72
From 65 to 84 years	567
85 years and over	100

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from investigative sites located in Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, South Korea, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Russia, Singapore, Slovakia, Spain, Switzerland, Taiwan, Turkey, UK, and Vietnam.

Pre-assignment

Screening details:

This reporting group includes all randomized and treated subjects (739).

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Brolucizumab 6 mg

Arm description:

Single intravitreal (IVT) injection of brolucizumab ophthalmic solution at Day 0, Week 4, and Week 8, followed by q8w/q12w maintenance regimen until study exit

Arm type	Experimental
Investigational medicinal product name	Brolucizumab ophthalmic solution
Investigational medicinal product code	
Other name	RTH258
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use, Ophthalmic use

Dosage and administration details:

Brolucizumab ophthalmic solution, 6 mg/50 µL dose, administered as a single IVT injection at Day 0, Week 4, and Week 8, followed by 1 injection every 8 weeks/1 injection every 12 weeks (q8w/q12w) maintenance regimen until study exit.

Arm title	Aflibercept 2 mg

Arm description:

Single IVT injection of aflibercept ophthalmic solution at Day 0, Week 4, and Week 8, followed by q8w maintenance regimen until study exit

Arm type	Active comparator
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	EYLEA®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use, Ophthalmic use

Dosage and administration details:

Aflibercept ophthalmic solution, 2 mg/50 µL dose, administered as a single IVT injection at Day 0, Week 4, and Week 8, followed by q8w maintenance regimen until study exit.

Number of subjects in period 1	Brolucizumab 6 mg	Aflibercept 2 mg
Started	370	369
Completed	342	329
Not completed	28	40
Adverse event, serious fatal	4	7
Consent withdrawn by subject	12	21
Physician decision	-	1
Adverse event, non-fatal	8	3
Lost to follow-up	1	6
Other - not specified	3	-
Lack of efficacy	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Brolucizumab 6 mg
Reporting group description:	
Single intravitreal (IVT) injection of brolucizumab ophthalmic solution at Day 0, Week 4, and Week 8, followed by q8w/q12w maintenance regimen until study exit	
Reporting group title	Aflibercept 2 mg
Reporting group description:	
Single IVT injection of aflibercept ophthalmic solution at Day 0, Week 4, and Week 8, followed by q8w maintenance regimen until study exit	

Reporting group values	Brolucizumab 6 mg	Aflibercept 2 mg	Total
Number of subjects	370	369	739
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	74.8	75.5	
standard deviation	± 8.58	± 7.87	-
Gender categorical Units: Subjects			
Female	210	212	422
Male	160	157	317

End points

End points reporting groups

Reporting group title	Brolucizumab 6 mg
Reporting group description:	
Single intravitreal (IVT) injection of brolucizumab ophthalmic solution at Day 0, Week 4, and Week 8, followed by q8w/q12w maintenance regimen until study exit	
Reporting group title	Aflibercept 2 mg
Reporting group description:	
Single IVT injection of aflibercept ophthalmic solution at Day 0, Week 4, and Week 8, followed by q8w maintenance regimen until study exit	

Primary: Change From Baseline in Best Corrected Visual Acuity (BCVA) (Letters Read) at Week 48 - Study Eye

End point title	Change From Baseline in Best Corrected Visual Acuity (BCVA) (Letters Read) at Week 48 - Study Eye
End point description:	
BCVA (with spectacles or other visual corrective devices) was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) testing at 4 meters and reported in letters read correctly. Baseline was defined as the last measurement prior to first treatment. An increase (gain) in letters read from the baseline assessment indicates improvement. One eye (study eye) contributed to the analysis. Full Analysis Set (FAS) - Last Observation Carried Forward (LOCF). Results reported up to Week 48 are based on the database locked for the primary analysis at Week 48.	
End point type	Primary
End point timeframe:	
Baseline, Week 48	

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	370[1]	369[2]		
Units: letters				
arithmetic mean (standard deviation)	6.9 (± 11.47)	7.6 (± 12.47)		

Notes:

[1] - Full Analysis Set (FAS) - Last Observation Carried Forward (LOCF)

[2] - Full Analysis Set (FAS) - Last Observation Carried Forward (LOCF)

Statistical analyses

Statistical analysis title	Change from BL in BCVA at Week 48 - Study Eye
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	739
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	ANOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.86

Notes:

[3] - The noninferiority margin was 4 letters.

[4] - 1-sided p-value reported. Hypothesis tested according to pre-specified hierarchical testing that ensures global type I error rate at 0.05. Analyzed using ANOVA model with baseline BCVA categories, age categories, and treatment as fixed effect factors

Secondary: Average Change From Baseline in BCVA (Letters Read) Over the Period Week 36 Through Week 48 - Study Eye

End point title	Average Change From Baseline in BCVA (Letters Read) Over the Period Week 36 Through Week 48 - Study Eye

End point description:

BCVA (with spectacles or other visual corrective devices) was assessed using ETDRS testing at 4 meters and reported in letters read correctly. Baseline was defined as the last measurement prior to first treatment. An increase (gain) in letters read from the baseline assessment indicates improvement. One eye (study eye) contributed to the analysis. Results reported up to Week 48 are based on the database locked for the primary analysis at Week 48.

End point type	Secondary

End point timeframe:

Baseline, Weeks 36, 40, 44, 48

End point values	Brolucizumab 6 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	370[5]	369[6]		
Units: letters				
arithmetic mean (standard deviation)	6.6 (± 11.10)	7.7 (± 11.81)		

Notes:

[5] - FAS - LOCF

[6] - FAS - LOCF

Statistical analyses

Statistical analysis title	Average Change From BL in BCVA - Weeks 36-48
Comparison groups	Brolucizumab 6 mg v Aflibercept 2 mg
Number of subjects included in analysis	739
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.0003 [8]
Method	ANOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.82

Notes:

[7] - The non-inferiority margin was 4 letters.

[8] - 1-sided p-value reported. Hypothesis tested according to pre-specified hierarchical testing that ensures global type I error rate at 0.05. Analyzed using ANOVA model with baseline BCVA categories, age categories, and treatment as fixed effect factors

Secondary: Proportion of Subjects With Positive q12 Treatment Status at Week 48

End point title	Proportion of Subjects With Positive q12 Treatment Status at Week 48[9]

End point description:

Positive q12 treatment status was defined as IVT injections per planned dosing regimen (one injection every 12 weeks "q12w", after the initial three loading injections every 4 weeks "q4w"). A disease activity assessment (DAA) was performed at pre-specified visits (Weeks 16, 20, 28, 32, 40, 44) to identify q8w need. The estimate for the proportion of subjects with a positive q12w status at Week 48 were derived from Kaplan-Meier time to event analyses for the event of first q8w need, applying event allocations (in case of lack of efficacy and/or lack of safety=efficacy/safety approach) and censoring as described in the SAP. Censored subjects were considered to be not anymore under risk for a q8 need identification at later visits. Corresponding 95% Confidence Intervals (CIs) were derived from the LOGLOG transformation. This outcome measure was pre-specified for brolucizumab 6 mg arm only.

End point type	Secondary

End point timeframe:

Weeks 16, 20, 28, 32, 40, 44, 48

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No hypothesis testing was performed.

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	370[10]			
Units: proportion of subjects				
number (confidence interval 95%)	0.5101 (0.4567 to 0.5610)			

Notes:

[10] - FAS - efficacy/safety approach

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Positive q12 Treatment Status at Week 48 Within the Subjects With no q8w Treatment Need During the Initial q12w Cycle

End point title	Proportion of Subjects With Positive q12 Treatment Status at Week 48 Within the Subjects With no q8w Treatment Need During the Initial q12w Cycle[11]

End point description:

Positive q12 treatment status was defined as IVT injections per planned dosing regimen (one injection every 12 weeks "q12w", after the initial three loading injections every 4 weeks "q4w"). A disease

activity assessment (DAA) was performed at pre-specified visits (Weeks 16, 20, 28, 32, 40, 44) to identify q8w need. The estimate for the proportion of subjects with a positive q12w status at Week 48 were derived from Kaplan-Meier time to event analyses for the event of first q8w need, applying event allocations (in case of lack of efficacy and/or lack of safety=efficacy/safety approach) and censoring as described in the SAP. Censored subjects were considered to be not anymore under risk for a q8 need identification at later visits. Corresponding 95% Confidence Intervals (CIs) were derived from the LOGLOG transformation. This outcome measure was pre-specified for brolucizumab 6 mg arm only.

End point type	Secondary

End point timeframe:

Weeks 16, 20, 28, 32, 40, 44, 48

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No hypothesis testing was performed.

End point values	Brolucizumab 6 mg			
Subject group type	Reporting group			
Number of subjects analysed	220[12]			
Units: proportion of subjects				
number (confidence interval 95%)	0.8170 (0.7582 to 0.8629)			

Notes:

[12] - FAS - efficacy/safety approach

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) were collected for the duration of enrollment in the study.

Adverse event reporting additional description:

AEs were obtained through solicited and spontaneous comments from subjects and through observations by the Investigator as outlined in the study protocol. This analysis population includes all subjects who received at least 1 IVT injection (Safety Analysis Set).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	RTH258 6mg

Reporting group description:

RTH258 6mg

Reporting group title	Aflibercept 2mg

Reporting group description:

Aflibercept 2mg

Serious adverse events	RTH258 6mg	Aflibercept 2mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	79 / 370 (21.35%)	89 / 369 (24.12%)	
number of deaths (all causes)	4	7	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast neoplasm			
subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colon cancer			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon neoplasm			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diffuse large B-cell lymphoma			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	2 / 370 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Hip surgery			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implantable defibrillator replacement			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein operation			

subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (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			
Cyst			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 370 (0.00%)	3 / 369 (0.81%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Pyrexia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			

subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (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			
Acute pulmonary oedema			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 370 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (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	1 / 370 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Charles Bonnet syndrome			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental fatigue			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood disorder due to a general medical condition			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoid personality disorder			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigation			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
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			
Cataract traumatic - Study eye			

subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Facial bones fracture			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 370 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 370 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
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	0 / 370 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb traumatic amputation			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	3 / 370 (0.81%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
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 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			

subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 370 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block right			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	2 / 370 (0.54%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Myocardial infarction			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parasystole			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
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	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 370 (0.00%)	4 / 369 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			
subjects affected / exposed	0 / 370 (0.00%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 370 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 370 (0.81%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 370 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
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 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Anterior chamber inflammation - Study eye			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness - Study eye			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry age-related macular degeneration - Study eye			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery embolism - Study eye			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion - Study eye			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery thrombosis - Study eye			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment - Study eye			

subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal pigment epithelial tear - Study eye			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear - Study eye			
subjects affected / exposed	2 / 370 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis - Study eye			
subjects affected / exposed	3 / 370 (0.81%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced - Study eye			
subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis haemorrhagic			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar hernia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 370 (0.54%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
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	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Neuropathic ulcer			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (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			
Acute prerenal failure			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary bladder polyp			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder rupture			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (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			
Arthralgia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 370 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column stenosis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (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	1 / 370 (0.27%)	2 / 369 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryocystitis - Study eye			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (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 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis - Study eye			

subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	2 / 370 (0.54%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 370 (0.54%)	8 / 369 (2.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (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	1 / 370 (0.27%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 369 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitamin D deficiency			

subjects affected / exposed	1 / 370 (0.27%)	0 / 369 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RTH258 6mg	Aflibercept 2mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	176 / 370 (47.57%)	194 / 369 (52.57%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	28 / 370 (7.57%)	25 / 369 (6.78%)	
occurrences (all)	34	28	
Eye disorders			
Cataract - Fellow eye			
subjects affected / exposed	7 / 370 (1.89%)	22 / 369 (5.96%)	
occurrences (all)	7	22	
Cataract - Study eye			
subjects affected / exposed	11 / 370 (2.97%)	43 / 369 (11.65%)	
occurrences (all)	11	43	
Conjunctival haemorrhage - Study eye			
subjects affected / exposed	17 / 370 (4.59%)	19 / 369 (5.15%)	
occurrences (all)	19	21	
Eye pain - Study eye			
subjects affected / exposed	13 / 370 (3.51%)	19 / 369 (5.15%)	
occurrences (all)	19	26	
Neovascular age-related macular degeneration - Fellow eye			
subjects affected / exposed	31 / 370 (8.38%)	32 / 369 (8.67%)	
occurrences (all)	33	32	
Visual acuity reduced - Study eye			
subjects affected / exposed	31 / 370 (8.38%)	25 / 369 (6.78%)	
occurrences (all)	38	38	
Musculoskeletal and connective tissue disorders			

Back pain			
subjects affected / exposed	16 / 370 (4.32%)	28 / 369 (7.59%)	
occurrences (all)	20	33	
Infections and infestations			
Bronchitis			
subjects affected / exposed	22 / 370 (5.95%)	20 / 369 (5.42%)	
occurrences (all)	31	23	
Influenza			
subjects affected / exposed	24 / 370 (6.49%)	27 / 369 (7.32%)	
occurrences (all)	24	29	
Nasopharyngitis			
subjects affected / exposed	43 / 370 (11.62%)	31 / 369 (8.40%)	
occurrences (all)	60	42	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2015	To clarify some inclusion/exclusion criteria and study procedures, and to allow unrestricted access to standard of care therapy for the fellow eye
10 February 2017	To allow ADA analysis of the samples collected from subjects treated with aflibercept 2 mg

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported