Clinical trial results:
A PHASE 2/3, RANDOMIZED, DOUBLE-MASKED, SHAM-CONTROLLED TRIAL OF QPI-1007 DELIVERED BY SINGLE OR MULTI-DOSE INTRAVITREAL INJECTION(S) TO SUBJECTS WITH ACUTE NONARTERITIC ANTERIOR ISCHEMIC OPTIC NEUROPATHY (NAION)

Summary

EudraCT number	2015-003079-31
Trial protocol	DE IT
Global end of trial date	14 June 2019

Results information

Result version number	v1 (current)
This version publication date	22 July 2021
First version publication date	22 July 2021

Trial information

Trial identification

Sponsor protocol code	QRK207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02341560
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Quark Pharmaceuticals, Inc.
Sponsor organisation address	7999 Gateway Boulevard, Suite 310, Newark, California , United States, 94560
Public contact	Clinical Operations, Quark Pharmaceuticals Inc., +1 510424020, dcafaro@quarkpharma.com
Scientific contact	Clinical Operations, Quark Pharmaceuticals Inc., +1 510424020, dcafaro@quarkpharma.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	14 June 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 June 2019
Global end of trial reached?	Yes
Global end of trial date	14 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To assess the safety and tolerability of QPI-1007 IVT injections in subjects with recent-onset NAION.
2. To determine the effect on visual function of QPI-1007 IVT injections in subjects with recent-onset NAION.

Protection of trial subjects:

The trial was completed according to the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2016
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	Germany: 23
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	China: 34
Country: Number of subjects enrolled	India: 111
Country: Number of subjects enrolled	Israel: 47
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	United States: 463
Worldwide total number of subjects	732
EEA total number of subjects	46

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)	480
From 65 to 84 years	252
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at a total of 80 sites, with sites in Australia, China, Germany, India, Israel, Italy, Singapore and the United States

Pre-assignment

Screening details:

A total of 1,092 subjects with symptoms indicative of NAION were screened, of which 732 were randomized and 725 received test treatment within 16 days of onset of symptoms.

Period 1

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

Blinding implementation details:

Site study staff conducting and evaluating all ophthalmic evaluations will be masked to the treatment assignment, except those staff who perform the 30-minute post-dose assessments. Only masked staff should perform assessment of AEs for causality and relatedness to study treatment. Masked staff may not perform any Pharmacy tasks that compromise or could potentially compromise the study masking. The pharmacist, Investigator administering study treatment, unmasked coordinator will be unmasked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 - ITT

Arm description:

Single dose regime, 1.5mg dose of QPI-1007 on day 1. Sham dose administered at months 2 and 4.

Arm type	Experimental
Investigational medicinal product name	QPI-1007
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

1.5 mg QPI-1007 dose. Preparation of QPI-1007 for administration should be done using aseptic techniques. The IVT injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate topical anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Arm title	Cohort 2 - ITT

Arm description:

Single dose regime. 3mg QPI-1007 administered on day 1. Sham administration on months 2 and 4.

Arm type	Experimental
Investigational medicinal product name	QPI-1007
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

3mg QPI-1007 dose. Preparation of QPI-1007 for administration should be done using aseptic techniques. The IVT injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate topical anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Arm title	Cohort 3 - ITT

Arm description:

Multiple dose regimen. 1.5 mg QPI-1007 dose on day 1, and months 2 and 4.

Arm type	Experimental
Investigational medicinal product name	QPI-1007
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

1.5mg QPI-1007 dose. Preparation of QPI-1007 for administration should be done using aseptic techniques. The IVT injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate topical anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Arm title	Cohort 4 - ITT

Arm description:

Multiple dose regimen. 3mg QPI-I007 administered on day 1, and months 2 and 4.

Arm type	Experimental
Investigational medicinal product name	QPI-1007
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

3mg QPI-1007 dose. Preparation of QPI-1007 for administration should be done using aseptic techniques. The IVT injection procedure should be carried out under controlled aseptic conditions, which include the use of sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate topical anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Arm title	Cohort 5 - ITT

Arm description:

Sham control.
For subjects receiving the sham-procedure no study drug was prepared but an empty syringe was used. The IVT injection was simulated by touching the eye with the blunt end of a syringe; the globe is not penetrated

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Cohort 1 - ITT	Cohort 2 - ITT	Cohort 3 - ITT
Started	81	81	191
Completed	75	74	102
Not completed	6	7	89
Consent withdrawn by subject	1	4	6
Physician decision	-	-	1
Adverse event, non-fatal	1	1	2
Other	-	-	-
Study Terminated by Sponsor	-	-	75
Lost to follow-up	3	2	3

Lack of efficacy	1	-	-
Protocol deviation	-	-	2

Number of subjects in period 1	Cohort 4 - ITT	Cohort 5 - ITT
Started	188	191
Completed	102	103
Not completed	86	88
Consent withdrawn by subject	4	3
Physician decision	-	-
Adverse event, non-fatal	-	2
Other	2	-
Study Terminated by Sponsor	76	77
Lost to follow-up	1	2
Lack of efficacy	-	3
Protocol deviation	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 - ITT
Reporting group description:	
Single dose regime, 1.5mg dose of QPI-1007 on day 1. Sham dose administered at months 2 and 4.	
Reporting group title	Cohort 2 - ITT
Reporting group description:	
Single dose regime. 3mg QPI-1007 administered on day 1. Sham administration on months 2 and 4.	
Reporting group title	Cohort 3 - ITT
Reporting group description:	
Multiple dose regimen. 1.5 mg QPI-1007 dose on day 1, and months 2 and 4.	
Reporting group title	Cohort 4 - ITT
Reporting group description:	
Multiple dose regimen. 3mg QPI-I007 administered on day 1, and months 2 and 4.	
Reporting group title	Cohort 5 - ITT
Reporting group description:	
Sham control. For subjects receiving the sham-procedure no study drug was prepared but an empty syringe was used. The IVT injection was simulated by touching the eye with the blunt end of a syringe; the globe is not penetrated	

Reporting group values	Cohort 1 - ITT	Cohort 2 - ITT	Cohort 3 - ITT
Number of subjects	81	81	191
Age categorical Units: Subjects			
Adults (18-64 years)	53	60	124
From 65-84 years	28	21	67
Age continuous Units: years			
arithmetic mean	61.2	60.3	61.7
full range (min-max)	50 to 80	50 to 77	50 to 80
Gender categorical Units: Subjects			
Female	25	33	58
Male	56	48	133

Reporting group values	Cohort 4 - ITT	Cohort 5 - ITT	Total
Number of subjects	188	191	732
Age categorical Units: Subjects			
Adults (18-64 years)	122	121	480
From 65-84 years	66	70	252
Age continuous Units: years			
arithmetic mean	61.3	61.7	
full range (min-max)	50 to 80	50 to 79	-

Gender categorical Units: Subjects			
Female	56	58	230
Male	132	133	502

Subject analysis sets

Subject analysis set title	Cohort 1 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Single dose regime, 1.5mg dose of QPI-1007 on day 1. Sham dose administered at months 2 and 4. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.

Subject analysis set title	Cohort 2 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Single dose regime. 3mg QPI-1007 administered on day 1. Sham administration on months 2 and 4. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.

Subject analysis set title	Cohort 3 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Multiple dose regimen. 1.5 mg QPI-1007 dose on day 1, and months 2 and 4. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.

Subject analysis set title	Cohort 4 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Multiple dose regimen. 3mg QPI-I007 administered on day 1, and months 2 and 4. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.

Subject analysis set title	Cohort 5 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Sham control. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.

Subject analysis set title	Cohort 1 - As treated
Subject analysis set type	Per protocol

Subject analysis set description:

Single dose regime, 1.5mg dose of QPI-1007 on day 1. Sham dose administered at months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Subject analysis set title	Cohort 2 - As treated
Subject analysis set type	Per protocol

Subject analysis set description:

Single dose regime. 3mg QPI-1007 administered on day 1. Sham administration on months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Subject analysis set title	Cohort 3 - As treated
Subject analysis set type	Per protocol

Subject analysis set description:

Multiple dose regimen. 1.5 mg QPI-1007 dose on day 1, and months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Subject analysis set title	Cohort 4 - As treated
Subject analysis set type	Per protocol

Subject analysis set description:

Multiple dose regimen. 3mg QPI-I007 administered on day 1, and months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Subject analysis set title	Cohort 5 - As treated

Subject analysis set type	Per protocol

Subject analysis set description:

Sham control. As treated analysis set includes all subjects who received the correct test treatment.

Reporting group values	Cohort 1 - mITT ≤ 12days	Cohort 2 - mITT ≤ 12days	Cohort 3 - mITT ≤ 12days
Number of subjects	101	100	168
Age categorical Units: Subjects			
Adults (18-64 years)	67	70	110
From 65-84 years	34	30	58
Age continuous Units: years arithmetic mean full range (min-max)			
Gender categorical Units: Subjects			
Female	29	38	54
Male	72	62	114

Reporting group values	Cohort 4 - mITT ≤ 12days	Cohort 5 - mITT ≤ 12days	Cohort 1 - As treated
Number of subjects	166	190	57
Age categorical Units: Subjects			
Adults (18-64 years)	111	120	
From 65-84 years	55	70	
Age continuous Units: years arithmetic mean full range (min-max)			61.3 50 to 80
Gender categorical Units: Subjects			
Female	49	58	16
Male	117	132	41

Reporting group values	Cohort 2 - As treated	Cohort 3 - As treated	Cohort 4 - As treated
Number of subjects	55	146	142
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous Units: years arithmetic mean full range (min-max)	61.0 50 to 80	61.5 50 to 80	60.9 50 to 80
Gender categorical Units: Subjects			
Female	18	46	41
Male	37	100	101

Reporting group values	Cohort 5 - As treated		

Number of subjects	144		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Age continuous Units: years arithmetic mean full range (min-max)	 61.8 50 to 79		
Gender categorical Units: Subjects			
Female Male	46 98		

End points

End points reporting groups

Reporting group title	Cohort 1 - ITT
Reporting group description:	
Single dose regime, 1.5mg dose of QPI-1007 on day 1. Sham dose administered at months 2 and 4.	
Reporting group title	Cohort 2 - ITT
Reporting group description:	
Single dose regime. 3mg QPI-1007 administered on day 1. Sham administration on months 2 and 4.	
Reporting group title	Cohort 3 - ITT
Reporting group description:	
Multiple dose regimen. 1.5 mg QPI-1007 dose on day 1, and months 2 and 4.	
Reporting group title	Cohort 4 - ITT
Reporting group description:	
Multiple dose regimen. 3mg QPI-I007 administered on day 1, and months 2 and 4.	
Reporting group title	Cohort 5 - ITT
Reporting group description:	
Sham control. For subjects receiving the sham-procedure no study drug was prepared but an empty syringe was used. The IVT injection was simulated by touching the eye with the blunt end of a syringe; the globe is not penetrated	
Subject analysis set title	Cohort 1 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Single dose regime, 1.5mg dose of QPI-1007 on day 1. Sham dose administered at months 2 and 4. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.	
Subject analysis set title	Cohort 2 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Single dose regime. 3mg QPI-1007 administered on day 1. Sham administration on months 2 and 4. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.	
Subject analysis set title	Cohort 3 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Multiple dose regimen. 1.5 mg QPI-1007 dose on day 1, and months 2 and 4. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.	
Subject analysis set title	Cohort 4 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Multiple dose regimen. 3mg QPI-I007 administered on day 1, and months 2 and 4. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.	
Subject analysis set title	Cohort 5 - mITT ≤ 12days
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Sham control. mITT ≤ 12days analysis set include subjects who were randomized within 12 days of the onset of symptoms.	
Subject analysis set title	Cohort 1 - As treated
Subject analysis set type	Per protocol
Subject analysis set description:	
Single dose regime, 1.5mg dose of QPI-1007 on day 1. Sham dose administered at months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.	
Subject analysis set title	Cohort 2 - As treated

Subject analysis set type	Per protocol

Subject analysis set description:

Single dose regime. 3mg QPI-1007 administered on day 1. Sham administration on months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Subject analysis set title	Cohort 3 - As treated
Subject analysis set type	Per protocol

Subject analysis set description:

Multiple dose regimen. 1.5 mg QPI-1007 dose on day 1, and months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Subject analysis set title	Cohort 4 - As treated
Subject analysis set type	Per protocol

Subject analysis set description:

Multiple dose regimen. 3mg QPI-I007 administered on day 1, and months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Subject analysis set title	Cohort 5 - As treated
Subject analysis set type	Per protocol

Subject analysis set description:

Sham control. As treated analysis set includes all subjects who received the correct test treatment.

Primary: Number of subjects who lose 15 letters or more in Best Corrected Visual Acuity (BCVA) score as measured by ETDRS visual acuity protocol in the study eye from Baseline to Month 6.

End point title	Number of subjects who lose 15 letters or more in Best Corrected Visual Acuity (BCVA) score as measured by ETDRS visual acuity protocol in the study eye from Baseline to Month 6.

End point description:

Number of subjects who lose 15 letters or more in BCVA at Month 6 from Baseline. Results given as number of patients who have altered BCVA.

End point type	Primary

End point timeframe:

6 months post treatment

End point values	Cohort 1 - mITT ≤ 12days	Cohort 2 - mITT ≤ 12days	Cohort 3 - mITT ≤ 12days	Cohort 4 - mITT ≤ 12days
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	57	55	146	142
Units: Subjects	17	17	23	27

End point values	Cohort 5 - mITT ≤ 12days			
Subject group type	Subject analysis set			
Number of subjects analysed	144			
Units: Subjects	21			

Statistical analyses

Statistical analysis title	Percentage difference from control
Comparison groups	Cohort 1 - mITT ≤ 12days v Cohort 5 - mITT ≤ 12days
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0217
Method	Regression, Logistic
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Percentage difference from control
Comparison groups	Cohort 2 - mITT ≤ 12days v Cohort 5 - mITT ≤ 12days
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0146
Method	Regression, Logistic
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Percentage difference from control
Comparison groups	Cohort 3 - mITT ≤ 12days v Cohort 5 - mITT ≤ 12days
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7808
Method	Regression, Logistic
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided

Statistical analysis title	Percentage difference from control
Comparison groups	Cohort 4 - mITT ≤ 12days v Cohort 5 - mITT ≤ 12days

Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293
Method	Regression, Logistic
Parameter estimate	Percentage difference
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs and SAEs will be recorded from the time of first study drug administration/sham procedure through 12 months post treatment or early termination

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Cohort 1 - As treated

Reporting group description:

Single dose regime, 1.5mg dose of QPI-1007 on day 1. Sham dose administered at months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Reporting group title	Cohort 2 - As treated

Reporting group description:

Single dose regime. 3mg QPI-1007 administered on day 1. Sham administration on months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Reporting group title	Cohort 3 - As treated

Reporting group description:

Multiple dose regimen. 1.5 mg QPI-1007 dose on day 1, and months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Reporting group title	Cohort 4 - As treated

Reporting group description:

Multiple dose regimen. 3mg QPI-I007 administered on day 1, and months 2 and 4. As treated analysis set includes all subjects who received the correct test treatment.

Reporting group title	Cohort 5 - As treated

Reporting group description:

Sham control. As treated analysis set includes all subjects who received the correct test treatment.

Serious adverse events	Cohort 1 - As treated	Cohort 2 - As treated	Cohort 3 - As treated
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 101 (10.89%)	17 / 100 (17.00%)	17 / 168 (10.12%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour haemorrhage			

subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic aneurysm	Additional description: Abdominal Aortic Aneurysm		
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental status changes	Additional description: Reaction to medication given for fall. reaction was altered mental state		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
C-Reactive Protein Increase			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus	Additional description: post operative		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract traumatic	Additional description: retraumatic cataract		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body in eye	Additional description: foreign body in cornea		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion	Additional description: Hemorrhagic contusion		

subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture	Additional description: fracture of left hip		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction	Additional description: non-ST segment elevation myocardial infarction		
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			

subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion	Additional description: Chronic total occlusion of the coronary artery		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			

subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual field defect			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia	Additional description: worsening of anaemia		
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo	Additional description: Vertigo of unknown etiology		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Vitreous floaters			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole	Additional description: Stage 4 macular hole		
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Age-related macular degeneration	Additional description: Wet age-related macular degeneration		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal perforation	Additional description: retraumatic corneal perforation		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic ischaemic neuropathy	Additional description: Progressive Anterior Optic Neuropathy Bilateral Sequential		
subjects affected / exposed	2 / 101 (1.98%)	2 / 100 (2.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blindness unilateral	Additional description: severe visual loss		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloedema	Additional description: Marked increase in Optic Nerve Edema OS due to NAION		
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photophobia	Additional description: Loss of vision to light perception OS		
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual impairment			

subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	2 / 101 (1.98%)	8 / 100 (8.00%)	6 / 168 (3.57%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Optic atrophy			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye haemorrhage			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Peptic ulcer			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive oesophagitis			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Intervertebral disc protrusion	Additional description: Prolapsed Inter vertebral disc		
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Urinary tract infection			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leptospirosis			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 4 - As treated	Cohort 5 - As treated	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 166 (13.25%)	19 / 190 (10.00%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm	Additional description: Abdominal Aortic Aneurysm		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
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 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes	Additional description: Reaction to medication given for fall. reaction was altered mental state		
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-Reactive Protein Increase			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus	Additional description: post operative		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract traumatic	Additional description: retraumatic cataract		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in eye	Additional description: foreign body in cornea		

subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion	Additional description: Hemorrhagic contusion		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture	Additional description: fracture of left hip		
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
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 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: non-ST segment elevation myocardial infarction		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			

subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion	Additional description: Chronic total occlusion of the coronary artery		
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (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 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular insufficiency			

subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: worsening of anaemia		
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo	Additional description: Vertigo of unknown etiology		

subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Vitreous floaters			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole	Additional description: Stage 4 macular hole		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Age-related macular degeneration	Additional description: Wet age-related macular degeneration		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal perforation	Additional description: retraumatic corneal perforation		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy	Additional description: Progressive Anterior Optic Neuropathy Bilateral Sequential		
subjects affected / exposed	4 / 166 (2.41%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness unilateral	Additional description: severe visual loss		
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema	Additional description: Marked increase in Optic Nerve Edema OS due to NAION		
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Photophobia	Additional description: Loss of vision to light perception OS		

subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	0 / 166 (0.00%)	2 / 190 (1.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	7 / 166 (4.22%)	9 / 190 (4.74%)	
occurrences causally related to treatment / all	0 / 7	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic atrophy			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Peptic ulcer			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive oesophagitis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion	Additional description: Prolapsed Inter vertebral disc		
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (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			
Bronchitis viral			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leptospirosis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			

subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Cohort 1 - As treated	Cohort 2 - As treated	Cohort 3 - As treated
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 101 (77.23%)	75 / 100 (75.00%)	133 / 168 (79.17%)
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	3 / 101 (2.97%)	2 / 100 (2.00%)	7 / 168 (4.17%)
occurrences (all)	3	2	7
Hypotension			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Hyperaemia			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Oral surgery			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	1 / 168 (0.60%)
occurrences (all)	0	2	1
Facial pain			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	1	1	1
Influenza like illness			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Glassy eyes			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Injection site pain			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Injection site discomfort			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Injection site erythema			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	2	0	0
Pain			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	1	0	2
Peripheral swelling			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	1 / 101 (0.99%)	4 / 100 (4.00%)	3 / 168 (1.79%)
occurrences (all)	1	4	3
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	2	0	0
Hypersensitivity			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Seasonal allergy			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1

Bronchitis			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	6 / 168 (3.57%)
occurrences (all)	1	1	6
Rhinitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Social circumstances			
Menopause			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Prostatitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 101 (1.98%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	2	1	0
Cough			
subjects affected / exposed	3 / 101 (2.97%)	2 / 100 (2.00%)	7 / 168 (4.17%)
occurrences (all)	3	2	7
Nasal congestion			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	3 / 168 (1.79%)
occurrences (all)	0	0	3
Epistaxis			

subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Hiccups			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Nasal oedema			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Nasal polyps			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Respiratory tract congestion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	3 / 168 (1.79%)
occurrences (all)	0	0	3
Paranasal sinus discomfort			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Sleep apnoea syndrome			
subjects affected / exposed	6 / 101 (5.94%)	4 / 100 (4.00%)	3 / 168 (1.79%)
occurrences (all)	6	4	3
Asthma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Upper airway obstruction			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract congestion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			

Anxiety			
subjects affected / exposed	3 / 101 (2.97%)	2 / 100 (2.00%)	2 / 168 (1.19%)
occurrences (all)	3	2	2
Depression			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	1	1	0
Stress			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Investigations			
Blood calcium increased			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Blood cholesterol increased			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	1	0	2
Blood homocysteine increased			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Blood pressure increased			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Blood urea increased			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	3 / 168 (1.79%)
occurrences (all)	0	0	3
Blood triglycerides increased			
subjects affected / exposed	4 / 101 (3.96%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	4	1	1
Injury, poisoning and procedural complications			
Toothache			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	4 / 168 (2.38%)
occurrences (all)	1	0	5
Tooth abscess			

subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Arthropod bite			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Conjunctival abrasion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Corneal abrasion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Contusion			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Foreign body in eye			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	1	1	0
Foot fracture			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Hand fracture			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Injection related reaction			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Injury			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Joint swelling			

subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	3 / 168 (1.79%)
occurrences (all)	0	0	3
Joint dislocation			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Limb injury			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Muscle rupture			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	0	0	2
Muscle strain			
subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	2	0	2
Lumbar vertebral fracture			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Product administration error			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Rib fracture			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Stress fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Skin laceration			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase			

increased			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Methylenetetrahydrofolate reductase gene mutation			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Left ventricular hypertrophy			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Cardiomyopathy			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Visual field defect			
subjects affected / exposed	3 / 101 (2.97%)	3 / 100 (3.00%)	4 / 168 (2.38%)
occurrences (all)	3	3	4
Nerve compression			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
anaemia			
subjects affected / exposed	1 / 101 (0.99%)	2 / 100 (2.00%)	0 / 168 (0.00%)
occurrences (all)	1	2	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	0	0	2
Tinnitus			

subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	2	0	1
Vertigo			
subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	1	1	0
Anterior chamber cell			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Blepharitis			
subjects affected / exposed	1 / 101 (0.99%)	2 / 100 (2.00%)	3 / 168 (1.79%)
occurrences (all)	1	2	3
Blepharospasm			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Cataract			
subjects affected / exposed	3 / 101 (2.97%)	2 / 100 (2.00%)	2 / 168 (1.19%)
occurrences (all)	3	2	2
Cataract nuclear			
subjects affected / exposed	1 / 101 (0.99%)	2 / 100 (2.00%)	1 / 168 (0.60%)
occurrences (all)	1	2	1
Cataract subcapsular			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Conjunctival haemorrhage			
subjects affected / exposed	13 / 101 (12.87%)	11 / 100 (11.00%)	24 / 168 (14.29%)
occurrences (all)	13	11	24
Conjunctival hyperaemia			
subjects affected / exposed	1 / 101 (0.99%)	3 / 100 (3.00%)	3 / 168 (1.79%)
occurrences (all)	1	3	3
Corneal epithelial microcysts			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0

Cyanopsia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Dermatochalasis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis allergic			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Cystoid macular oedema			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Diplopia			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	2 / 168 (1.19%)
occurrences (all)	1	1	2
Dry eye			
subjects affected / exposed	3 / 101 (2.97%)	6 / 100 (6.00%)	7 / 168 (4.17%)
occurrences (all)	3	6	7
Eye disorder			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Eye allergy			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Eye irritation			
subjects affected / exposed	2 / 101 (1.98%)	3 / 100 (3.00%)	4 / 168 (2.38%)
occurrences (all)	2	3	4
Eye pain			
subjects affected / exposed	5 / 101 (4.95%)	5 / 100 (5.00%)	19 / 168 (11.31%)
occurrences (all)	5	5	19
Eye swelling			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	0	0	2
Eyelid oedema			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	0 / 168 (0.00%)
occurrences (all)	0	2	0

Eyelid pain			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Eye pruritus			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	1 / 168 (0.60%)
occurrences (all)	0	2	1
swelling of the eyelid			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Eyelid irritation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Foreign body sensation in eyes			
subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	2	0	0
Glare			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Macular fibrosis			
subjects affected / exposed	1 / 101 (0.99%)	2 / 100 (2.00%)	0 / 168 (0.00%)
occurrences (all)	1	2	0
Iritis			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	2 / 168 (1.19%)
occurrences (all)	0	2	2
Macular detachment			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Macular oedema			
subjects affected / exposed	1 / 101 (0.99%)	3 / 100 (3.00%)	2 / 168 (1.19%)
occurrences (all)	1	3	2
Metamorphopsia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1

Meibomian gland dysfunction			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Ocular discomfort			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	1	1	0
Ocular hypertension			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	0	0	1
Ocular hyperaemia			
subjects affected / exposed	2 / 101 (1.98%)	1 / 100 (1.00%)	3 / 168 (1.79%)
occurrences (all)	2	1	3
Optic atrophy			
subjects affected / exposed	2 / 101 (1.98%)	2 / 100 (2.00%)	2 / 168 (1.19%)
occurrences (all)	2	2	2
Optic disc disorder			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Optic disc haemorrhage			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	5 / 168 (2.98%)
occurrences (all)	0	0	5
Optic ischaemic neuropathy			
subjects affected / exposed	7 / 101 (6.93%)	4 / 100 (4.00%)	2 / 168 (1.19%)
occurrences (all)	7	4	2
Optic nerve disorder			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Optic nerve sheath haemorrhage			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	0	0	2
Papilloedema			
subjects affected / exposed	6 / 101 (5.94%)	3 / 100 (3.00%)	3 / 168 (1.79%)
occurrences (all)	6	3	3
Photopsia			
subjects affected / exposed	3 / 101 (2.97%)	2 / 100 (2.00%)	1 / 168 (0.60%)
occurrences (all)	3	2	1

Photophobia			
subjects affected / exposed	0 / 101 (0.00%)	3 / 100 (3.00%)	1 / 168 (0.60%)
occurrences (all)	0	3	1
Punctate keratitis			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	6 / 168 (3.57%)
occurrences (all)	1	1	6
Pupillary reflex impaired			
subjects affected / exposed	2 / 101 (1.98%)	2 / 100 (2.00%)	1 / 168 (0.60%)
occurrences (all)	2	2	1
Retinal degeneration			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	1	1	0
Retinal disorder			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	0	0	1
Retinal detachment			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Retinal exudates			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	1	0	2
Retinal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	2 / 100 (2.00%)	2 / 168 (1.19%)
occurrences (all)	1	2	2
Retinal neovascularisation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Retinoschisis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	2 / 101 (1.98%)	1 / 100 (1.00%)	2 / 168 (1.19%)
occurrences (all)	2	1	2
Visual acuity reduced			
subjects affected / exposed	11 / 101 (10.89%)	18 / 100 (18.00%)	15 / 168 (8.93%)
occurrences (all)	11	18	15

Visual impairment			
subjects affected / exposed	5 / 101 (4.95%)	6 / 100 (6.00%)	7 / 168 (4.17%)
occurrences (all)	5	6	7
Vitreous detachment			
subjects affected / exposed	0 / 101 (0.00%)	3 / 100 (3.00%)	2 / 168 (1.19%)
occurrences (all)	0	3	2
Vitreous floaters			
subjects affected / exposed	5 / 101 (4.95%)	8 / 100 (8.00%)	5 / 168 (2.98%)
occurrences (all)	5	8	5
Vitritis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Vitreous opacities			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Asthenopia			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Abdominal pain			
subjects affected / exposed	2 / 101 (1.98%)	3 / 100 (3.00%)	0 / 168 (0.00%)
occurrences (all)	2	3	0
Abdominal pain upper			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	3 / 168 (1.79%)
occurrences (all)	0	1	3
Chronic gastritis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Dental caries			

subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	2	0	0
Duodenal polyp			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Inflammatory bowel disease			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Paraesthesia oral			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	2	0	1
Vomiting			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Blister			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Dermatitis allergic			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Psoriasis			

subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Eczema			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Actinic keratosis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	2 / 101 (1.98%)	1 / 100 (1.00%)	2 / 168 (1.19%)
occurrences (all)	2	1	2
Rash pruritic			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Skin lesion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Impaired driving ability			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Splinter haemorrhages			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Diabetic retinopathy			

subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	2 / 168 (1.19%)
occurrences (all)	1	1	2
Vitreous degeneration			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Bronchiolitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	1 / 101 (0.99%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Cystitis			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis viral			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Eye infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis viral			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	1	0	1
Helicobacter infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0

Herpes zoster			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Hordeolum			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	1 / 168 (0.60%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	2 / 101 (1.98%)	2 / 100 (2.00%)	5 / 168 (2.98%)
occurrences (all)	2	2	5
Lower respiratory tract infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Labyrinthitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
lung infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Nail infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	8 / 101 (7.92%)	11 / 100 (11.00%)	18 / 168 (10.71%)
occurrences (all)	8	11	18
Otitis externa			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	0	0	2
Oral herpes			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	0	0	2
Pneumonia			
subjects affected / exposed	0 / 101 (0.00%)	2 / 100 (2.00%)	1 / 168 (0.60%)
occurrences (all)	0	2	1

Postoperative wound infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Root canal infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	6 / 101 (5.94%)	0 / 100 (0.00%)	9 / 168 (5.36%)
occurrences (all)	6	0	9
Tooth infection			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	2	0	2
Urinary tract infection			
subjects affected / exposed	4 / 101 (3.96%)	1 / 100 (1.00%)	1 / 168 (0.60%)
occurrences (all)	4	1	1
Viral infection			
subjects affected / exposed	2 / 101 (1.98%)	0 / 100 (0.00%)	0 / 168 (0.00%)
occurrences (all)	2	0	0
Vulval abscess			
subjects affected / exposed	0 / 101 (0.00%)	1 / 100 (1.00%)	0 / 168 (0.00%)
occurrences (all)	0	1	0
Chemical burns of eye			
subjects affected / exposed	0 / 101 (0.00%)	0 / 100 (0.00%)	2 / 168 (1.19%)
occurrences (all)	0	0	2

Non-serious adverse events	Cohort 4 - As treated	Cohort 5 - As treated	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 166 (75.30%)	134 / 190 (70.53%)	
Vascular disorders			
Arterial occlusive disease			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Hypertension			

subjects affected / exposed	10 / 166 (6.02%)	10 / 190 (5.26%)	
occurrences (all)	10	10	
Hypotension			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Hyperaemia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Oral surgery			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 166 (1.20%)	4 / 190 (2.11%)	
occurrences (all)	2	4	
Facial pain			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Influenza like illness			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Glassy eyes			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Injection site pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Injection site discomfort			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Injection site erythema			

subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Peripheral swelling			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 166 (0.60%)	2 / 190 (1.05%)	
occurrences (all)	1	2	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Hypersensitivity			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Seasonal allergy			
subjects affected / exposed	2 / 166 (1.20%)	5 / 190 (2.63%)	
occurrences (all)	2	5	
Bronchitis			
subjects affected / exposed	4 / 166 (2.41%)	2 / 190 (1.05%)	
occurrences (all)	4	2	
Rhinitis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Social circumstances			
Menopause			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Prostatitis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	5 / 166 (3.01%)	4 / 190 (2.11%)	
occurrences (all)	5	4	
Nasal congestion			
subjects affected / exposed	1 / 166 (0.60%)	2 / 190 (1.05%)	
occurrences (all)	1	2	
Epistaxis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Nasal oedema			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Nasal polyps			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Respiratory tract congestion			
subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			

subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Paranasal sinus discomfort			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Sleep apnoea syndrome			
subjects affected / exposed	5 / 166 (3.01%)	5 / 190 (2.63%)	
occurrences (all)	5	5	
Asthma			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Upper airway obstruction			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract congestion			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 166 (0.60%)	2 / 190 (1.05%)	
occurrences (all)	1	2	
Depression			
subjects affected / exposed	0 / 166 (0.00%)	3 / 190 (1.58%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Investigations			
Blood calcium increased			

subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Blood cholesterol increased			
subjects affected / exposed	2 / 166 (1.20%)	5 / 190 (2.63%)	
occurrences (all)	2	5	
Blood homocysteine increased			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Blood pressure increased			
subjects affected / exposed	2 / 166 (1.20%)	3 / 190 (1.58%)	
occurrences (all)	2	3	
Blood urea increased			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	0 / 166 (0.00%)	3 / 190 (1.58%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Toothache			
subjects affected / exposed	3 / 166 (1.81%)	1 / 190 (0.53%)	
occurrences (all)	3	1	
Tooth abscess			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Arthropod bite			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Conjunctival abrasion			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Corneal abrasion			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Contusion			

subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)		
occurrences (all)	2	0		
Fall				
subjects affected / exposed	1 / 166 (0.60%)	3 / 190 (1.58%)		
occurrences (all)	1	3		
Foreign body in eye				
subjects affected / exposed	1 / 166 (0.60%)	2 / 190 (1.05%)		
occurrences (all)	1	2		
Ligament sprain				
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)		
occurrences (all)	0	1		
Foot fracture				
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)		
occurrences (all)	1	0		
Hand fracture				
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)		
occurrences (all)	0	0		
Injection related reaction				
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)		
occurrences (all)	1	0		
Injury				
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)		
occurrences (all)	0	0		
Joint swelling				
subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)		
occurrences (all)	2	0		
Joint injury				
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)		
occurrences (all)	0	1		
Joint dislocation				
subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)		
occurrences (all)	2	0		
Limb injury				
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)		
occurrences (all)	1	0		
Muscle rupture				

subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Muscle strain			
subjects affected / exposed	1 / 166 (0.60%)	3 / 190 (1.58%)	
occurrences (all)	1	3	
Lumbar vertebral fracture			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Product administration error			
subjects affected / exposed	2 / 166 (1.20%)	2 / 190 (1.05%)	
occurrences (all)	2	2	
Rib fracture			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Stress fracture			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Skin laceration			
subjects affected / exposed	1 / 166 (0.60%)	3 / 190 (1.58%)	
occurrences (all)	1	3	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 166 (1.20%)	2 / 190 (1.05%)	
occurrences (all)	2	2	
Congenital, familial and genetic disorders			
Methylenetetrahydrofolate reductase gene mutation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Left ventricular hypertrophy			

subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Cardiomyopathy			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Visual field defect			
subjects affected / exposed	10 / 166 (6.02%)	4 / 190 (2.11%)	
occurrences (all)	10	4	
Nerve compression			
subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
anaemia			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Ear pain			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Anterior chamber cell			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Blepharitis			

subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Blepharospasm			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Cataract			
subjects affected / exposed	3 / 166 (1.81%)	4 / 190 (2.11%)	
occurrences (all)	3	4	
Cataract nuclear			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Cataract subcapsular			
subjects affected / exposed	3 / 166 (1.81%)	0 / 190 (0.00%)	
occurrences (all)	3	0	
Conjunctival haemorrhage			
subjects affected / exposed	18 / 166 (10.84%)	4 / 190 (2.11%)	
occurrences (all)	18	4	
Conjunctival hyperaemia			
subjects affected / exposed	0 / 166 (0.00%)	4 / 190 (2.11%)	
occurrences (all)	0	4	
Corneal epithelial microcysts			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Cyanopsia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Dermatochalasis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Conjunctivitis allergic			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Cystoid macular oedema			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Diplopia			

subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	6 / 166 (3.61%)	6 / 190 (3.16%)	
occurrences (all)	6	6	
Eye disorder			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Eye allergy			
subjects affected / exposed	1 / 166 (0.60%)	2 / 190 (1.05%)	
occurrences (all)	1	2	
Eye irritation			
subjects affected / exposed	8 / 166 (4.82%)	1 / 190 (0.53%)	
occurrences (all)	8	1	
Eye pain			
subjects affected / exposed	8 / 166 (4.82%)	10 / 190 (5.26%)	
occurrences (all)	8	10	
Eye swelling			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Eyelid pain			
subjects affected / exposed	0 / 166 (0.00%)	10 / 190 (5.26%)	
occurrences (all)	0	10	
Eye pruritus			
subjects affected / exposed	2 / 166 (1.20%)	6 / 190 (3.16%)	
occurrences (all)	2	6	
swelling of the eyelid			
subjects affected / exposed	3 / 166 (1.81%)	0 / 190 (0.00%)	
occurrences (all)	3	0	
Eyelid irritation			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Foreign body sensation in eyes			

subjects affected / exposed	1 / 166 (0.60%)	2 / 190 (1.05%)	
occurrences (all)	1	2	
Glare			
subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)	
occurrences (all)	2	0	
Macular fibrosis			
subjects affected / exposed	3 / 166 (1.81%)	1 / 190 (0.53%)	
occurrences (all)	3	1	
Iritis			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Lacrimation increased			
subjects affected / exposed	4 / 166 (2.41%)	4 / 190 (2.11%)	
occurrences (all)	4	4	
Macular detachment			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Macular oedema			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Metamorphopsia			
subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)	
occurrences (all)	2	0	
Meibomian gland dysfunction			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Ocular discomfort			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Ocular hypertension			
subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)	
occurrences (all)	2	0	
Ocular hyperaemia			
subjects affected / exposed	3 / 166 (1.81%)	6 / 190 (3.16%)	
occurrences (all)	3	6	
Optic atrophy			

subjects affected / exposed	5 / 166 (3.01%)	1 / 190 (0.53%)	
occurrences (all)	5	1	
Optic disc disorder			
subjects affected / exposed	1 / 166 (0.60%)	2 / 190 (1.05%)	
occurrences (all)	1	2	
Optic disc haemorrhage			
subjects affected / exposed	3 / 166 (1.81%)	0 / 190 (0.00%)	
occurrences (all)	3	0	
Optic ischaemic neuropathy			
subjects affected / exposed	10 / 166 (6.02%)	8 / 190 (4.21%)	
occurrences (all)	10	8	
Optic nerve disorder			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Optic nerve sheath haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Papilloedema			
subjects affected / exposed	9 / 166 (5.42%)	2 / 190 (1.05%)	
occurrences (all)	9	2	
Photopsia			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Photophobia			
subjects affected / exposed	4 / 166 (2.41%)	0 / 190 (0.00%)	
occurrences (all)	4	0	
Punctate keratitis			
subjects affected / exposed	4 / 166 (2.41%)	4 / 190 (2.11%)	
occurrences (all)	4	4	
Pupillary reflex impaired			
subjects affected / exposed	3 / 166 (1.81%)	1 / 190 (0.53%)	
occurrences (all)	3	1	
Retinal degeneration			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Retinal disorder			

subjects affected / exposed	2 / 166 (1.20%)	2 / 190 (1.05%)	
occurrences (all)	2	2	
Retinal detachment			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Retinal exudates			
subjects affected / exposed	2 / 166 (1.20%)	4 / 190 (2.11%)	
occurrences (all)	2	4	
Retinal haemorrhage			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Retinal neovascularisation			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Retinoschisis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Vision blurred			
subjects affected / exposed	4 / 166 (2.41%)	5 / 190 (2.63%)	
occurrences (all)	4	5	
Visual acuity reduced			
subjects affected / exposed	21 / 166 (12.65%)	18 / 190 (9.47%)	
occurrences (all)	21	18	
Visual impairment			
subjects affected / exposed	3 / 166 (1.81%)	4 / 190 (2.11%)	
occurrences (all)	3	4	
Vitreous detachment			
subjects affected / exposed	8 / 166 (4.82%)	7 / 190 (3.68%)	
occurrences (all)	8	7	
Vitreous floaters			
subjects affected / exposed	5 / 166 (3.01%)	3 / 190 (1.58%)	
occurrences (all)	5	3	
Vitritis			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Vitreous opacities			

subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Asthenopia			
subjects affected / exposed	2 / 166 (1.20%)	0 / 190 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 166 (1.81%)	2 / 190 (1.05%)	
occurrences (all)	3	2	
Abdominal pain			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Abdominal pain upper			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Chronic gastritis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Dental caries			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Duodenal polyp			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Inflammatory bowel disease			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Paraesthesia oral			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Rectal haemorrhage			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	

Nausea			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed	1 / 166 (0.60%)	2 / 190 (1.05%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Blister			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Dermatitis allergic			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Psoriasis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Eczema			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Actinic keratosis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Rash pruritic			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Pruritus			

subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Impaired driving ability			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Splinter haemorrhages			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Diabetic retinopathy			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Vitreous degeneration			
subjects affected / exposed	0 / 166 (0.00%)	2 / 190 (1.05%)	
occurrences (all)	0	2	
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Bronchiolitis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Cellulitis			
subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			

subjects affected / exposed	3 / 166 (1.81%)	3 / 190 (1.58%)	
occurrences (all)	3	3	
Cystitis			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Conjunctivitis viral			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Eye infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Gastroenteritis viral			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Helicobacter infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Herpes zoster			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Hordeolum			
subjects affected / exposed	2 / 166 (1.20%)	1 / 190 (0.53%)	
occurrences (all)	2	1	
Influenza			
subjects affected / exposed	2 / 166 (1.20%)	5 / 190 (2.63%)	
occurrences (all)	2	5	
Lower respiratory tract infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Labyrinthitis			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
lung infection			

subjects affected / exposed	1 / 166 (0.60%)	0 / 190 (0.00%)	
occurrences (all)	1	0	
Nail infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	12 / 166 (7.23%)	17 / 190 (8.95%)	
occurrences (all)	12	17	
Otitis externa			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	1 / 166 (0.60%)	1 / 190 (0.53%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	0 / 166 (0.00%)	2 / 190 (1.05%)	
occurrences (all)	0	2	
Postoperative wound infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Root canal infection			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Sinusitis			
subjects affected / exposed	5 / 166 (3.01%)	12 / 190 (6.32%)	
occurrences (all)	5	12	
Tooth infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	10 / 166 (6.02%)	5 / 190 (2.63%)	
occurrences (all)	10	5	
Urinary tract infection			

subjects affected / exposed	4 / 166 (2.41%)	2 / 190 (1.05%)	
occurrences (all)	4	2	
Viral infection			
subjects affected / exposed	0 / 166 (0.00%)	1 / 190 (0.53%)	
occurrences (all)	0	1	
Vulval abscess			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	
Chemical burns of eye			
subjects affected / exposed	0 / 166 (0.00%)	0 / 190 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2014	Added language to note this is a Pivotal Phase II/III study Language added from provided reference regarding disease population. Revised confirmation of eligibility for subjects <50 and >80 years of age. Language modified to exclude subjects previously exposed to QPI-1007. Language added to note VF assessment at Month 2. Language added for AE and SAE reporting to cover local regulatory authority requirements for global protocol Language added for concomitant treatment collection to cover local regulatory authority requirements for global protocol. Added language to note that confirmation of enrollment eligibility to occur prior to Day 0. Language added for SAE notification Optional interim analysis deleted due to revised study design. Language added to global protocol to capture video consent requirements where applicable, per local regulatory authorities.

11 March 2015	Clarified language to note dose options. Corrected language as not all subjects will receive three bi-monthly IVT injections. Interim analysis plan for the study was modified to include a futility analysis after 40 subjects in each treatment group complete Month 6 visit. Month 9 study visit added for safety follow-up. Language added to define afferent papillary defect inclusion criteria; Enrollment Adjudication Board removed and inclusion criteria confirmed that subjects must be 50 to 80 years of age. Added language to note Indian requirements, criterion for study eye, low dose aspirin therapy dose is per local standard. Added language to clarify exclusion criterion for diabetic retinopathy, concomitant disease and uveitis Language Added to allow basal cell carcinoma allowed only if adequately treated. Removal of FSH testing and ECG testing. Reference to diluted study drug removed as study drug will not be diluted. Correction of sample size determination and primary end point analysis, added multiple comparison procedure and futility analysis. Language added to note Key Secondary Endpoints and Secondary Efficacy Endpoints. Overall Summary of Related AEs table removed Contrast sensitivity added as an ophthalmologic assessment at Day 0 and Months 2, 4, 6, 9, and 12/ET. CRP and Westergren sedimentation rate added Entry criteria added for study eye, Instructions added for Day 0/Post-dose. Information added for adverse events in case of early treatment discontinuation Allocation of treatment groups defined for randomization Information on sensitivity and subgroup analysis was included.
09 September 2015	Changed all references for concomitant medications and treatments collection from 7 days to 14 days. Removed “differential” from WBC laboratory collection. Changed all references of Day “0” to Day “1” and Day “7” to Day “8.” Added Europe to increase diversity of patient population. Adverse events, regardless of severity, must be collected for the entire study for all regions Added ganglion cell layer to Secondary objective. Study changed from 4-arm to 5-arm study. As such, study design was updated Reduced Screening window from 28 days to 14 days, Removed Contrast Sensitivity procedure/exam from protocol. Removed all mentions of 96 hours screening period and related references that stated Screening and Day 1 could occur on the same day.

16 October 2015	Updated: to reflect current understanding of disease process and number of subjects to accommodate recalculation of statistical hypothesis. Increased total number of study sites from 50 to 60. Removed aspirin requirement as background therapy. Added "OCT image and VF pattern compatible with the diagnosis of NAION, as determined by a Central Reading Center" image and VF pattern compatibility" to Screening visit task list. Changed inclusion criterion to allow Best-Corrected Visual Acuity score in the study eye to be better than or equal to 15 letter score without an upper limit Added exclusion criterion: "history of amiodarone use in the 12 months prior to the Day 1/Randomization visit." and "NAION secondary to acute blood loss' and "any intravitreal injection within 3 months prior to Day 1 in the study eye only:" and "diffuse pale swelling of the optic disc." and "bilateral (simultaneous) disc swelling Additional exclusion criteria added included: "Visual Field exclusions at Screening Visit (inconclusive visual fields should be sent to the Reading Center for adjudication) Updated study background to include new information and related references Added information regarding QRK208 study, 5th dosing cohort added in Changed "other efficacy endpoints." Allows for Screening and Day 1 to occur on same day. Change made to provide better understanding of per-visit procedures as not all procedures occur at all visits.

06 October 2016	To explain purpose of and plan for newly-added sub-study. Clarification of global site distribution Clarification that there will be an earlier safety look, in addition to the already-listed interim analysis to be conducted after 40 subjects per group complete their Month 6 visit. It is not always the injecting physician who performs the 30-minute post-dose evaluations. Per German Regulatory Authority recommendation, removed barrier method as acceptable method of birth control Clarification of excluded ophthalmic surgeries. Clarification that subjects may be excluded by any visual field exclusions listed; subjects not required to meet ALL VF exclusions in order to be excluded. Clarified only study eye relevant to this criterion. Clarification that mild blepharitis, although considered an inflammatory condition, is NOT exclusionary. Correction to clarify potential subjects may be lactating and may not be actively nursing (lactating and nursing are not inclusive of one another). PDE5 inhibitors use is a risk for developing NAION and should not be used during the study. Updated to include new terms and correct existing list, to provide current information and status of QRK208 study. Spot size III using SITA standard 24-2 protocol is not done at Day 1, so this endpoint needs to be measured from Screening. Reduced requirement to avoid patient fatigue. Clarified spot size III requirement by name (previous version did not specify spot size).
15 March 2018	Sample size adjustment. The sample size has been recalculated to be consistent with the observed 20% overall rate of subjects losing 15-letters or more in visual acuity from 106 subjects to 213. Added language that another DMC will occur due to increased sample size Addition of ERG (for China sites only) to global protocol for Day 1 Pre-Dose, Month 2, and Month 6. Defined when 24-hour period starts (at first procedure after ICF, so any procedure after ICF). Added language found elsewhere in the protocol related to preferred time frame for study drug administration. Change type of stopper for study drug vial to "FuroTec-coated," instead of "Teflon-coated." Added statement that after the interim analysis, subjects already enrolled in the dropped regimen will continue until they have completed study participation Replaced duplicate IA information (already present in Sections 10.2 and 10.9) with definition of DMC purpose.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported