



Clinical trial results:

A Phase 2b/3 Multicenter, Randomized, Double-Masked, Dose-Ranging Study Comparing the Efficacy and Safety of Emixustat Hydrochloride (ACU-4429) with Placebo for the Treatment of Geographic Atrophy Associated with Dry Age-Related Macular Degeneration

Summary

EudraCT number	2012-004952-12
Trial protocol	DE
Global end of trial date	15 April 2016

Results information

Result version number	v1 (current)
This version publication date	18 September 2021
First version publication date	18 September 2021

Trial information

Trial identification

Sponsor protocol code	4429-202
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01802866
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Acucela Inc.
Sponsor organisation address	600 University Street, Suite 2900, Seattle, United States, 98101
Public contact	Acucela Clinical Trials Helpdesk, Acucela Inc., +1 2068058310, clinicaltrials@acucela.com
Scientific contact	Acucela Clinical Trials Helpdesk, Acucela Inc., 2068058300 2068058310, clinicaltrials@acucela.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	15 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 April 2016
Global end of trial reached?	Yes
Global end of trial date	15 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if ACU-4429 reduces the rate of progression of geographic atrophy (GA) compared to placebo in subjects with dry age-related macular degeneration (AMD).

Protection of trial subjects:

All subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 January 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	United States: 451
Worldwide total number of subjects	508
EEA total number of subjects	57

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)	28
From 65 to 84 years	382
85 years and over	98

Subject disposition

Recruitment

Recruitment details:

A total of 503 subjects were randomized and received study drug at 49 sites in the United States and 7 sites in Germany from February 2013 to April 2016.

Pre-assignment

Screening details:

A total of 968 subjects were screened, and 508 subjects were randomized. The most common reason for failing screening was the total area of GA not meeting an inclusion criterion (n = 219/460 screen failures).

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, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Emixustat 2.5 mg

Arm description:

Subjects took one oral tablet of emixustat 2.5 mg per day for 24 months.

Arm type	Experimental
Investigational medicinal product name	emixustat hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Emixustat 2.5 mg oral tablet taken once daily

Arm title	Emixustat 5 mg
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Arm description:

Subjects took one oral tablet of emixustat 5 mg per day for 24 months.

Arm type	Experimental
Investigational medicinal product name	emixustat hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Emixustat 5 mg oral tablet taken once daily

Arm title	Emixustat 10 mg
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Arm description:

Subjects took one oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months.

Arm type	Experimental
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Investigational medicinal product name	emixustat hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months.

Arm title	Placebo
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Arm description:

Subjects took one oral tablet of placebo per day for 24 months.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 tablet taken by mouth each day

Number of subjects in period 1	Emixustat 2.5 mg	Emixustat 5 mg	Emixustat 10 mg
Started	134	135	103
Completed	78	81	53
Not completed	56	54	50
Adverse event, serious fatal	3	2	1
Physician decision	1	-	-
Consent withdrawn by subject	16	8	9
Randomized in error, did not receive study drug	1	-	-
Adverse event, non-fatal	33	44	39
Lost to follow-up	2	-	1

Number of subjects in period 1	Placebo
Started	136
Completed	108
Not completed	28
Adverse event, serious fatal	-
Physician decision	2
Consent withdrawn by subject	6
Randomized in error, did not receive study drug	3
Adverse event, non-fatal	15
Lost to follow-up	2

Baseline characteristics

Reporting groups

Reporting group title	Emixustat 2.5 mg
Reporting group description: Subjects took one oral tablet of emixustat 2.5 mg per day for 24 months.	
Reporting group title	Emixustat 5 mg
Reporting group description: Subjects took one oral tablet of emixustat 5 mg per day for 24 months.	
Reporting group title	Emixustat 10 mg
Reporting group description: Subjects took one oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months.	
Reporting group title	Placebo
Reporting group description: Subjects took one oral tablet of placebo per day for 24 months.	

Reporting group values	Emixustat 2.5 mg	Emixustat 5 mg	Emixustat 10 mg
Number of subjects	134	135	103
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	78.2	78.2	77.2
standard deviation	± 7.11	± 7.79	± 7.96
Gender categorical Units: Subjects			
Female	79	73	61
Male	55	62	42

Reporting group values	Placebo	Total	
Number of subjects	136	508	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	

Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	77.1		
standard deviation	± 8.13	-	
Gender categorical			
Units: Subjects			
Female	77	290	
Male	59	218	

End points

End points reporting groups

Reporting group title	Emixustat 2.5 mg
Reporting group description: Subjects took one oral tablet of emixustat 2.5 mg per day for 24 months.	
Reporting group title	Emixustat 5 mg
Reporting group description: Subjects took one oral tablet of emixustat 5 mg per day for 24 months.	
Reporting group title	Emixustat 10 mg
Reporting group description: Subjects took one oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months.	
Reporting group title	Placebo
Reporting group description: Subjects took one oral tablet of placebo per day for 24 months.	

Primary: Mean rate of change from Baseline in the total area of geographic atrophy in the study eye

End point title	Mean rate of change from Baseline in the total area of geographic atrophy in the study eye
End point description:	
End point type	Primary
End point timeframe: 24 Months	

End point values	Emixustat 2.5 mg	Emixustat 5 mg	Emixustat 10 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	133	134	103	133
Units: mm ² per year				
least squares mean (standard error)	1.69 (± 0.115)	1.83 (± 0.116)	1.84 (± 0.143)	1.69 (± 0.108)

Statistical analyses

Statistical analysis title	Least square mean difference against placebo
Comparison groups	Emixustat 2.5 mg v Emixustat 5 mg v Emixustat 10 mg v Placebo

Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.81 ^[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.5
Variability estimate	Standard error of the mean
Dispersion value	0.18

Notes:

[1] - 2.5 mg group vs. placebo group -- p = 0.99

5 mg group vs. placebo group -- p = 0.81

10 mg group vs. placebo group -- p = 0.81

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 months

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Emixustat 2.5 mg
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Reporting group description:

Subjects took one oral tablet of emixustat 2.5 mg per day for 24 months.

Reporting group title	Emixustat 5 mg
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Reporting group description:

Subjects took one oral tablet of emixustat 5 mg per day for 24 months.

Reporting group title	Emixustat 10 mg
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Reporting group description:

Subjects took one oral tablet of emixustat 5 mg per day for 1 month, then one oral tablet of emixustat 7.5 mg per day for 1 month, and then one oral tablet of emixustat 10 mg per day for 22 months.

Reporting group title	Placebo
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Reporting group description:

Subjects took one oral tablet of placebo per day for 24 months.

Serious adverse events	Emixustat 2.5 mg	Emixustat 5 mg	Emixustat 10 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 133 (25.56%)	41 / 134 (30.60%)	20 / 103 (19.42%)
number of deaths (all causes)	3	2	1
number of deaths resulting from adverse events	3	2	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	2 / 133 (1.50%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer recurrent			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Lung adenocarcinoma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Lung cancer metastatic			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Prostate cancer recurrent			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salivary gland cancer			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Breast cancer metastatic			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Small cell lung cancer limited stage			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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			
Hypotension			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Peripheral artery occlusion			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Accelerated hypertension			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Temporal arteritis			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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			
Asthenia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Death			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Reproductive system and breast disorders			
Cystocele			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adnexa uteri mass			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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			
Chronic obstructive pulmonary disease			

subjects affected / exposed	3 / 133 (2.26%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	2 / 133 (1.50%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Pleural effusion			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
hypoxia			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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			
Cardiac murmur			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Transaminases increased			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 133 (0.00%)	6 / 134 (4.48%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 7	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	1 / 133 (0.75%)	2 / 134 (1.49%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 133 (0.00%)	2 / 134 (1.49%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 133 (0.75%)	1 / 134 (0.75%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cervical vertebral fracture			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Concussion			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delayed recovery from anaesthesia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Infusion related reaction			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Lumbar vertebral fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
pubis fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Rib fracture			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Spinal compression fracture			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Subdural haematoma			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid injury			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Facial bones fracture			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Tendon rupture			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 133 (2.26%)	1 / 134 (0.75%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	2 / 133 (1.50%)	1 / 134 (0.75%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sinus node dysfunction			
subjects affected / exposed	1 / 133 (0.75%)	1 / 134 (0.75%)	0 / 103 (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
Angina unstable			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
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 arrest			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Coronary artery stenosis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Ischaemic cardiomyopathy			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Angina pectoris			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Atrioventricular block			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Ventricular tachycardia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 133 (1.50%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			

subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Dizziness			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Seizure			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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			
subjects affected / exposed	3 / 133 (2.26%)	1 / 134 (0.75%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Ear and labyrinth disorders			

Vertigo positional subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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			
Optic ischaemic neuropathy subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Optic neuropathy subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Retinal artery occlusion subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Gastrointestinal disorders			
Small intestinal obstruction subjects affected / exposed	0 / 133 (0.00%)	2 / 134 (1.49%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Gastric ulcer subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Intestinal obstruction			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Pancreatitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Inguinal hernia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Intra-abdominal haematoma			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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 / 133 (0.00%)	1 / 134 (0.75%)	2 / 103 (1.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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

Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 133 (1.50%)	2 / 134 (1.49%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Back pain			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Spondylolisthesis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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			
Pneumonia			
subjects affected / exposed	2 / 133 (1.50%)	2 / 134 (1.49%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 133 (1.50%)	2 / 134 (1.49%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Appendicitis perforated			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Bronchitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Bronchopulmonary aspergillosis allergic			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Diverticulitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Endocarditis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Enterocolitis infectious			

subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Influenza			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Pneumonia pseudomonal			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	1 / 103 (0.97%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 133 (0.00%)	1 / 134 (0.75%)	0 / 103 (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
Streptococcal sepsis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (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
Appendicitis			

subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Escherichia sepsis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Escherichia urinary tract infection			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Herpes zoster			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Urinary tract infection			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 134 (0.00%)	0 / 103 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 133 (0.00%)	0 / 134 (0.00%)	0 / 103 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 133 (22.56%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal adenocarcinoma			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Laryngeal cancer recurrent			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung adenocarcinoma			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lung cancer metastatic subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer recurrent subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Salivary gland cancer subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer metastatic subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small cell lung cancer limited stage subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Orthostatic hypotension subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral artery occlusion			

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Accelerated hypertension			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Temporal arteritis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Cystocele			

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Adnexa uteri mass			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea exertional			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
hypoxia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Cardiac murmur			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transaminases increased			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Road traffic accident				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cervical vertebral fracture				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Delayed recovery from anaesthesia				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
pubis fracture				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib fracture				

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal compression fracture			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eyelid injury			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial bones fracture			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tendon rupture			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus node dysfunction			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angina unstable			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic valve incompetence			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic valve stenosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery stenosis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sinus bradycardia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrioventricular block			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			

subjects affected / exposed	4 / 133 (3.01%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carotid artery stenosis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coagulopathy			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Optic neuropathy			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal artery occlusion			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diverticulum intestinal haemorrhagic subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intra-abdominal haematoma			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Ureterolithiasis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	4 / 133 (3.01%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Spinal pain			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 133 (2.26%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Sepsis				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis perforated				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchopulmonary aspergillosis allergic				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 133 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				

subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocarditis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parainfluenzae virus infection			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia pseudomonal			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis acute			

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Streptococcal sepsis			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 133 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Emixustat 2.5 mg	Emixustat 5 mg	Emixustat 10 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	127 / 133 (95.49%)	131 / 134 (97.76%)	101 / 103 (98.06%)
Investigations			
Visual acuity tests abnormal			
subjects affected / exposed	9 / 133 (6.77%)	19 / 134 (14.18%)	14 / 103 (13.59%)
occurrences (all)	9	25	16
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 133 (5.26%)	14 / 134 (10.45%)	8 / 103 (7.77%)
occurrences (all)	7	16	13
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 133 (9.02%)	11 / 134 (8.21%)	5 / 103 (4.85%)
occurrences (all)	13	14	6
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 133 (4.51%)	3 / 134 (2.24%)	0 / 103 (0.00%)
occurrences (all)	6	4	0
Nervous system disorders			
Visual field defect			
subjects affected / exposed	7 / 133 (5.26%)	10 / 134 (7.46%)	12 / 103 (11.65%)
occurrences (all)	8	13	13
Headache			
subjects affected / exposed	5 / 133 (3.76%)	11 / 134 (8.21%)	6 / 103 (5.83%)
occurrences (all)	6	13	8
Dizziness			
subjects affected / exposed	5 / 133 (3.76%)	7 / 134 (5.22%)	2 / 103 (1.94%)
occurrences (all)	5	9	2
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	7 / 133 (5.26%) 7	4 / 134 (2.99%) 4	5 / 103 (4.85%) 6
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	6 / 133 (4.51%) 7	2 / 134 (1.49%) 2	1 / 103 (0.97%) 1
Eye disorders Delayed dark adaptation subjects affected / exposed occurrences (all)	48 / 133 (36.09%) 56	88 / 134 (65.67%) 105	69 / 103 (66.99%) 87
Chromatopsia subjects affected / exposed occurrences (all)	13 / 133 (9.77%) 13	30 / 134 (22.39%) 35	22 / 103 (21.36%) 23
Visual impairment subjects affected / exposed occurrences (all)	12 / 133 (9.02%) 14	25 / 134 (18.66%) 42	20 / 103 (19.42%) 25
Erythropsia subjects affected / exposed occurrences (all)	12 / 133 (9.02%) 15	26 / 134 (19.40%) 33	16 / 103 (15.53%) 19
Visual acuity reduced subjects affected / exposed occurrences (all)	18 / 133 (13.53%) 22	18 / 134 (13.43%) 22	13 / 103 (12.62%) 15
Vision blurred subjects affected / exposed occurrences (all)	10 / 133 (7.52%) 10	17 / 134 (12.69%) 18	16 / 103 (15.53%) 18
Choroidal neovascularisation subjects affected / exposed occurrences (all)	17 / 133 (12.78%) 19	10 / 134 (7.46%) 11	8 / 103 (7.77%) 10
Retinal haemorrhage subjects affected / exposed occurrences (all)	8 / 133 (6.02%) 10	15 / 134 (11.19%) 16	8 / 103 (7.77%) 10
Posterior capsule opacification subjects affected / exposed occurrences (all)	5 / 133 (3.76%) 6	13 / 134 (9.70%) 16	9 / 103 (8.74%) 11
Vitreous detachment			

subjects affected / exposed occurrences (all)	10 / 133 (7.52%) 12	10 / 134 (7.46%) 11	5 / 103 (4.85%) 5
Cataract nuclear subjects affected / exposed occurrences (all)	9 / 133 (6.77%) 13	11 / 134 (8.21%) 16	4 / 103 (3.88%) 4
Xanthopsia subjects affected / exposed occurrences (all)	2 / 133 (1.50%) 3	10 / 134 (7.46%) 10	9 / 103 (8.74%) 9
Night blindness subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 4	3 / 134 (2.24%) 3	10 / 103 (9.71%) 14
Cataract cortical subjects affected / exposed occurrences (all)	6 / 133 (4.51%) 11	6 / 134 (4.48%) 9	4 / 103 (3.88%) 7
Blepharitis subjects affected / exposed occurrences (all)	2 / 133 (1.50%) 2	7 / 134 (5.22%) 8	3 / 103 (2.91%) 3
Cyanopsia subjects affected / exposed occurrences (all)	2 / 133 (1.50%) 2	9 / 134 (6.72%) 9	1 / 103 (0.97%) 1
Dry age-related macular degeneration subjects affected / exposed occurrences (all)	3 / 133 (2.26%) 3	2 / 134 (1.49%) 2	6 / 103 (5.83%) 6
Punctate keratitis subjects affected / exposed occurrences (all)	3 / 133 (2.26%) 3	3 / 134 (2.24%) 3	3 / 103 (2.91%) 3
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 5	6 / 134 (4.48%) 6	5 / 103 (4.85%) 6
Diarrhoea subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 4	6 / 134 (4.48%) 7	2 / 103 (1.94%) 2
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	8 / 133 (6.02%) 10	7 / 134 (5.22%) 7	3 / 103 (2.91%) 3
Musculoskeletal and connective tissue disorders			
Back pain subjects affected / exposed occurrences (all)	7 / 133 (5.26%) 7	5 / 134 (3.73%) 6	6 / 103 (5.83%) 6
Arthralgia subjects affected / exposed occurrences (all)	2 / 133 (1.50%) 3	6 / 134 (4.48%) 8	2 / 103 (1.94%) 2
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	15 / 133 (11.28%) 21	12 / 134 (8.96%) 12	7 / 103 (6.80%) 8
Bronchitis subjects affected / exposed occurrences (all)	11 / 133 (8.27%) 12	5 / 134 (3.73%) 5	8 / 103 (7.77%) 8
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 133 (5.26%) 12	4 / 134 (2.99%) 6	6 / 103 (5.83%) 7
Herpes zoster subjects affected / exposed occurrences (all)	2 / 133 (1.50%) 2	1 / 134 (0.75%) 1	2 / 103 (1.94%) 2

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	127 / 133 (95.49%)		
Investigations			
Visual acuity tests abnormal subjects affected / exposed occurrences (all)	9 / 133 (6.77%) 9		
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	20 / 133 (15.04%) 26		
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	17 / 133 (12.78%) 20		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	7 / 133 (5.26%) 8		
Nervous system disorders Visual field defect subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	2 / 133 (1.50%) 2 13 / 133 (9.77%) 18 9 / 133 (6.77%) 11		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 133 (0.75%) 1		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	14 / 133 (10.53%) 17		
Eye disorders Delayed dark adaptation subjects affected / exposed occurrences (all) Chromatopsia subjects affected / exposed occurrences (all) Visual impairment subjects affected / exposed occurrences (all) Erythropsia	13 / 133 (9.77%) 15 4 / 133 (3.01%) 4 19 / 133 (14.29%) 32		

subjects affected / exposed	6 / 133 (4.51%)		
occurrences (all)	6		
Visual acuity reduced			
subjects affected / exposed	18 / 133 (13.53%)		
occurrences (all)	24		
Vision blurred			
subjects affected / exposed	10 / 133 (7.52%)		
occurrences (all)	11		
Choroidal neovascularisation			
subjects affected / exposed	17 / 133 (12.78%)		
occurrences (all)	30		
Retinal haemorrhage			
subjects affected / exposed	11 / 133 (8.27%)		
occurrences (all)	15		
Posterior capsule opacification			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	10		
Vitreous detachment			
subjects affected / exposed	11 / 133 (8.27%)		
occurrences (all)	14		
Cataract nuclear			
subjects affected / exposed	13 / 133 (9.77%)		
occurrences (all)	22		
Xanthopsia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences (all)	1		
Night blindness			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences (all)	1		
Cataract cortical			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	9		
Blepharitis			
subjects affected / exposed	4 / 133 (3.01%)		
occurrences (all)	5		
Cyanopsia			

subjects affected / exposed 0 / 133 (0.00%) occurrences (all) 0			
Dry age-related macular degeneration subjects affected / exposed 6 / 133 (4.51%) occurrences (all) 6			
Punctate keratitis subjects affected / exposed 7 / 133 (5.26%) occurrences (all) 9			
Gastrointestinal disorders Nausea subjects affected / exposed 11 / 133 (8.27%) occurrences (all) 12			
Diarrhoea subjects affected / exposed 15 / 133 (11.28%) occurrences (all) 25			
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed 12 / 133 (9.02%) occurrences (all) 13			
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed 5 / 133 (3.76%) occurrences (all) 8			
Arthralgia subjects affected / exposed 7 / 133 (5.26%) occurrences (all) 8			
Infections and infestations Nasopharyngitis subjects affected / exposed 27 / 133 (20.30%) occurrences (all) 38			
Bronchitis subjects affected / exposed 8 / 133 (6.02%) occurrences (all) 8			
Urinary tract infection			

subjects affected / exposed	17 / 133 (12.78%)		
occurrences (all)	18		
Herpes zoster			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 March 2013	Added exclusion of subjects with known allergy to active pharmaceutical ingredient or excipients
03 June 2013	Added further details to several exclusion criteria. Clarified that subjects who develop choroidal neovascularization or who are unmasked must be withdrawn from the study. Clarified prohibited concomitant medications.
07 November 2013	Added intraocular pressure and low luminance visual acuity to more visits. Instituted unscheduled visits to be performed in instances of decreased visual acuity.
17 December 2013	Increased sample size.
01 October 2014	Omitted interim analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29716784>