



Clinical trial results:

A Phase 2b Randomized, Double-Masked, Controlled Trial to Assess the Safety and Efficacy of Intravitreal Administration of Zimura™ (Anti-C5 Aptamer) in Subjects with Geographic Atrophy Secondary to Dry Age-Related Macular Degeneration

Summary

EudraCT number	2015-003991-56
Trial protocol	HU LV EE HR
Global end of trial date	23 April 2020

Results information

Result version number	v1 (current)
This version publication date	15 July 2022
First version publication date	15 July 2022

Trial information

Trial identification

Sponsor protocol code	OPH2003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02686658
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IVERIC bio, Inc.
Sponsor organisation address	1249 South River Road, Suite 107, Cranbury, United States, NJ 08512
Public contact	Medical Director, IVERIC bio, Inc., clinicaltrials@ivericbio.com
Scientific contact	Medical Director, IVERIC bio, Inc., clinicaltrials@ivericbio.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	19 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2019
Global end of trial reached?	Yes
Global end of trial date	23 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of this study were to evaluate the safety and efficacy of Zimura™ intravitreal administration when administered in subjects with geographic atrophy secondary to age-related macular degeneration (AMD). The study design was based on the screening study methodology presented in Fleming and Richardson 2004. By pre-specification, Screening analysis was performed to assess whether the effect of Zimura on the mean rate of GA growth was plausibly more efficacious (or reliably more efficacious) than that of the Sham control on the mean rate of GA growth over 12 months.

Protection of trial subjects:

Before initiation of the study, the protocol and the patient informed consent provisions were reviewed and approved by the appropriate Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) for each of the centers involved in the study according to national or local regulations and in accordance with the United States (US) Food and Drug Administration (FDA) Title 21, Code of Federal Regulations Parts 56.107 through 56.115, the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) guidelines (Committee for Proprietary Medicinal Products/ICH/135/95), or local laws. Study initiation at each site began only after receiving written approval from the IEC/IRB. The protocol amendments were reviewed and approved by the appropriate IECs or IRBs for each of the centers.

The study was conducted in full compliance with the principles of the Declaration of Helsinki, as adopted in 1964 by the 18th World Medical Assembly and amended in Tokyo, Venice, Hong Kong, South Africa, and Scotland, and in compliance with the respective law and regulations of the country in which the research was conducted. In addition, the study was performed in line with the principles outlined in the Guideline for GCP (ICH E6), the ICH Tripartite Guideline (May 1997), and US FDA regulations.

Prior to study entry, all patients were informed fully of the nature and aims of the study. Ample time was provided for patients to read the patient information sheet and ask any questions regarding the investigational drug. Patients were informed that their participation was voluntary and that they could withdraw from the study at any time for any reason without incurring any penalty or withholding of treatment on the part of the investigator. Before receiving any treatment related to this study, all patients provided their written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 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	Croatia: 5
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Hungary: 42
Country: Number of subjects enrolled	Latvia: 4

Country: Number of subjects enrolled	United States: 218
Country: Number of subjects enrolled	Israel: 8
Worldwide total number of subjects	286
EEA total number of subjects	60

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)	24
From 65 to 84 years	190
85 years and over	72

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Inclusion: age ≥ 50 years, geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

Exclusion: evidence of choroidal neovascularization (CNV) in either eye, GA secondary to any condition other than AMD, prior treatment for AMD or any prior intravitreal treatment

Period 1

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

Arms

Are arms mutually exclusive?	No
Arm title	Zimura 1 mg (part 1)

Arm description: -

Arm type	Experimental
Investigational medicinal product name	avacincaptad pegol
Investigational medicinal product code	ARC1905
Other name	Zimura
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Monthly administration of Zimura 1 mg/eye.

Arm title	Zimura 2 mg (Combined part 1 + part 2)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	avacincaptad pegol
Investigational medicinal product code	ARC1905
Other name	Zimura
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Part 1: Monthly administration of Zimura 2 mg/eye

Part 2: Monthly administration of Zimura 2mg/eye plus sham to maintain study masking

Arm title	Zimura 4 mg (part 2)
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	avacincaptad pegol
Investigational medicinal product code	ARC1905
Other name	Zimura
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Monthly administration of Zimura 4 mg/eye (administered as 2 IVT injections of Zimura 2mg/eye).

Arm title	Sham (Combined part 1 + part 2)
Arm description: -	
Arm type	Sham injection
No investigational medicinal product assigned in this arm	
Arm title	Sham (part 2)
Arm description: -	
Arm type	Sham injection
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Zimura 1 mg (part 1)	Zimura 2 mg (Combined part 1 + part 2)	Zimura 4 mg (part 2)
Started	26	67	83
Completed	24	55	58
Not completed	2	12	25
Consent withdrawn by subject	1	6	13
Physician decision	-	1	2
Adverse event, non-fatal	-	-	1
Death	-	-	1
Sponsor decision	1	5	8
Lost to follow-up	-	-	-

Number of subjects in period 1	Sham (Combined part 1 + part 2)	Sham (part 2)
Started	110	84
Completed	96	75
Not completed	14	9
Consent withdrawn by subject	8	5
Physician decision	1	1
Adverse event, non-fatal	1	-
Death	1	1
Sponsor decision	2	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	Zimura 1 mg (part 1)
Reporting group description: -	
Reporting group title	Zimura 2 mg (Combined part 1 + part 2)
Reporting group description: -	
Reporting group title	Zimura 4 mg (part 2)
Reporting group description: -	
Reporting group title	Sham (Combined part 1 + part 2)
Reporting group description: -	
Reporting group title	Sham (part 2)
Reporting group description: -	

Reporting group values	Zimura 1 mg (part 1)	Zimura 2 mg (Combined part 1 + part 2)	Zimura 4 mg (part 2)
Number of subjects	26	67	83
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	10	5
From 65-84 years	22	34	57
85 years and over	1	23	21
Age continuous Units: years			
arithmetic mean	73.8	78.8	79.2
standard deviation	± 7.97	± 10.22	± 8.31
Gender categorical Units: Subjects			
Female	15	45	58
Male	11	22	25
Ethnicity Units: Subjects			
Not Hispanic or Latino	25	66	82
Hispanic or Latino	1	1	1
Race Units: Subjects			
American Indian / Alaska Native	0	0	0
Black or African American	0	0	0
Asian	1	0	0
Native Hawaiian / Pacific Islander	0	0	0
White	25	67	82

Other	0	0	1
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Reporting group values	Sham (Combined part 1 + part 2)	Sham (part 2)	Total
Number of subjects	110	84	286
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	4	24
From 65-84 years	77	60	190
85 years and over	27	20	72
Age continuous Units: years			
arithmetic mean	78.2	78.2	
standard deviation	± 8.82	± 8.98	-
Gender categorical Units: Subjects			
Female	79	61	197
Male	31	23	89
Ethnicity Units: Subjects			
Not Hispanic or Latino	108	83	281
Hispanic or Latino	2	1	5
Race Units: Subjects			
American Indian / Alaska Native	0	0	0
Black or African American	1	1	1
Asian	0	0	1
Native Hawaiian / Pacific Islander	0	0	0
White	107	82	281
Other	2	1	3

End points

End points reporting groups

Reporting group title	Zimura 1 mg (part 1)
Reporting group description: -	
Reporting group title	Zimura 2 mg (Combined part 1 + part 2)
Reporting group description: -	
Reporting group title	Zimura 4 mg (part 2)
Reporting group description: -	
Reporting group title	Sham (Combined part 1 + part 2)
Reporting group description: -	
Reporting group title	Sham (part 2)
Reporting group description: -	

Primary: Change in Geographic Atrophy

End point title	Change in Geographic Atrophy ^[1]
End point description:	Mean rate of change in GA measured by fundus autofluorescence (FAF)
End point type	Primary
End point timeframe:	From baseline to Month 12.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Comparison of Zimura 1 mg vs. Sham was not part of the primary endpoint.

End point values	Zimura 2 mg (Combined part 1 + part 2)	Zimura 4 mg (part 2)	Sham (Combined part 1 + part 2)	Sham (part 2)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	83	110	84
Units: rate				
least squares mean (standard error)				
Month 12	0.292 (± 0.077)	0.321 (± 0.074)	0.402 (± 0.075)	0.444 (± 0.072)

Statistical analyses

Statistical analysis title	Zimura 2 mg compared to Sham - Month 12
Comparison groups	Zimura 2 mg (Combined part 1 + part 2) v Sham (Combined part 1 + part 2)
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0072
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	0.19

Statistical analysis title	Zimura 4 mg compared to Sham - Month 12
Comparison groups	Zimura 4 mg (part 2) v Sham (part 2)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.124
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.038
upper limit	0.209

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until End of Study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Zimura 1 mg
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Reporting group description: -

Reporting group title	Zimura 2 mg (Combined part 1 + part 2)
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Reporting group description: -

Reporting group title	Zimura 4 mg
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Reporting group description: -

Reporting group title	Sham (Combined part 1 + part 2)
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Reporting group description: -

Serious adverse events	Zimura 1 mg	Zimura 2 mg (Combined part 1 + part 2)	Zimura 4 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 26 (11.54%)	12 / 67 (17.91%)	21 / 83 (25.30%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Metastases to bone			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer stage IV			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Lung cancer metastatic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Metastases to adrenals			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Metastases to central nervous system			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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			
Subclavian artery stenosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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

Non-cardiac chest pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 distress			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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			
Anxiety			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Hallucination			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Injury, poisoning and procedural complications			
Femur fracture			

subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Hip fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Ulna fracture			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Head injury			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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			
Acute myocardial infarction			

subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve stenosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
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 extrasystoles			
subjects affected / exposed	1 / 26 (3.85%)	0 / 67 (0.00%)	0 / 83 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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			
Cerebrovascular accident			
subjects affected / exposed	1 / 26 (3.85%)	1 / 67 (1.49%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Dizziness			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cerebral infarction			

subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Cerebral haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 radiculopathy			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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			
Iron deficiency anaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Retinal detachment			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
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 disorders			

Colitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
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 necrosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
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 / 26 (3.85%)	0 / 67 (0.00%)	0 / 83 (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 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Abdominal hernia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Appendiceal mucocoele			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Faecaloma			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 haemorrhage			

subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Large intestinal stenosis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 intestinal obstruction			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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 stone			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
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 / 26 (0.00%)	1 / 67 (1.49%)	0 / 83 (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
Cholecystitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 26 (3.85%)	0 / 67 (0.00%)	0 / 83 (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 spinal stenosis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 67 (0.00%)	0 / 83 (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 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Osteoarthritis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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	0 / 26 (0.00%)	1 / 67 (1.49%)	3 / 83 (3.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 67 (2.99%)	0 / 83 (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
Sepsis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	2 / 83 (2.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			

subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	1 / 83 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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			
Hyperglycaemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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
Hyponatraemia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 67 (0.00%)	0 / 83 (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	Sham (Combined part 1 + part 2)		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 110 (25.45%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			

subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases to bone				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer stage IV				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung cancer metastatic				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung neoplasm malignant				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to adrenals				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma metastatic				

subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Subclavian artery stenosis			
subjects affected / exposed	1 / 110 (0.91%)		
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 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory distress			

subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hallucination			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	0 / 110 (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 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Ulna fracture			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mitral valve stenosis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular extrasystoles			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Cerebrovascular accident				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic cerebral infarction				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar radiculopathy				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				

Iron deficiency anaemia			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal necrosis			
subjects affected / exposed	0 / 110 (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 / 110 (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 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal hernia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Appendiceal mucocoele				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Large intestinal stenosis				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 110 (0.91%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile duct stone				
subjects affected / exposed	0 / 110 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholelithiasis				

subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Sepsis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Escherichia urinary tract infection			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Groin abscess			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			

subjects affected / exposed	1 / 110 (0.91%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Zimura 1 mg	Zimura 2 mg (Combined part 1 + part 2)	Zimura 4 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 26 (50.00%)	47 / 67 (70.15%)	66 / 83 (79.52%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 26 (3.85%)	6 / 67 (8.96%)	19 / 83 (22.89%)
occurrences (all)	2	15	19
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 26 (0.00%)	9 / 67 (13.43%)	6 / 83 (7.23%)
occurrences (all)	0	11	6
Laceration			
subjects affected / exposed	0 / 26 (0.00%)	3 / 67 (4.48%)	0 / 83 (0.00%)
occurrences (all)	0	3	0
Contusion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	2 / 83 (2.41%)
occurrences (all)	0	1	2
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 26 (0.00%)	1 / 67 (1.49%)	3 / 83 (3.61%)
occurrences (all)	0	1	3
Nervous system disorders			
Dementia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 67 (4.48%)	0 / 83 (0.00%)
occurrences (all)	0	3	0
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	2 / 26 (7.69%)	11 / 67 (16.42%)	28 / 83 (33.73%)
occurrences (all)	2	40	28
Neovascular age-related macular			

degeneration			
subjects affected / exposed	3 / 26 (11.54%)	9 / 67 (13.43%)	11 / 83 (13.25%)
occurrences (all)	3	10	11
Conjunctival hyperaemia			
subjects affected / exposed	0 / 26 (0.00%)	3 / 67 (4.48%)	9 / 83 (10.84%)
occurrences (all)	0	14	9
Punctate keratitis			
subjects affected / exposed	0 / 26 (0.00%)	4 / 67 (5.97%)	6 / 83 (7.23%)
occurrences (all)	0	7	6
Eye pain			
subjects affected / exposed	0 / 26 (0.00%)	2 / 67 (2.99%)	8 / 83 (9.64%)
occurrences (all)	0	2	8
Vitreous detachment			
subjects affected / exposed	3 / 26 (11.54%)	2 / 67 (2.99%)	4 / 83 (4.82%)
occurrences (all)	4	3	4
Cataract			
subjects affected / exposed	2 / 26 (7.69%)	4 / 67 (5.97%)	2 / 83 (2.41%)
occurrences (all)	4	4	2
Visual acuity reduced			
subjects affected / exposed	0 / 26 (0.00%)	4 / 67 (5.97%)	3 / 83 (3.61%)
occurrences (all)	0	4	3
Conjunctival oedema			
subjects affected / exposed	0 / 26 (0.00%)	2 / 67 (2.99%)	5 / 83 (6.02%)
occurrences (all)	0	7	5
Choroidal neovascularisation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 67 (0.00%)	5 / 83 (6.02%)
occurrences (all)	1	0	5
Eye irritation			
subjects affected / exposed	0 / 26 (0.00%)	3 / 67 (4.48%)	2 / 83 (2.41%)
occurrences (all)	0	6	2
Posterior capsule opacification			
subjects affected / exposed	0 / 26 (0.00%)	2 / 67 (2.99%)	0 / 83 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			

Osteoarthritis subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	1 / 67 (1.49%) 1	0 / 83 (0.00%) 0
Spinal column stenosis subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	0 / 67 (0.00%) 0	0 / 83 (0.00%) 0
Infections and infestations			
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 4	7 / 67 (10.45%) 10	10 / 83 (12.05%) 10
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 2	7 / 67 (10.45%) 8	3 / 83 (3.61%) 3
Sinusitis subjects affected / exposed occurrences (all)	2 / 26 (7.69%) 2	3 / 67 (4.48%) 3	3 / 83 (3.61%) 3
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	2 / 67 (2.99%) 2	5 / 83 (6.02%) 5
Influenza subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	3 / 67 (4.48%) 3	0 / 83 (0.00%) 0
Rhinitis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	3 / 67 (4.48%) 3	0 / 83 (0.00%) 0
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0	0 / 67 (0.00%) 0	1 / 83 (1.20%) 1

Non-serious adverse events	Sham (Combined part 1 + part 2)		
Total subjects affected by non-serious adverse events subjects affected / exposed	59 / 110 (53.64%)		
Investigations			
Intraocular pressure increased subjects affected / exposed occurrences (all)	1 / 110 (0.91%) 2		

Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Laceration subjects affected / exposed occurrences (all) Contusion subjects affected / exposed occurrences (all)	7 / 110 (6.36%) 7 3 / 110 (2.73%) 3 2 / 110 (1.82%) 2		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	4 / 110 (3.64%) 4		
Nervous system disorders Dementia subjects affected / exposed occurrences (all)	0 / 110 (0.00%) 0		
Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all) Neovascular age-related macular degeneration subjects affected / exposed occurrences (all) Conjunctival hyperaemia subjects affected / exposed occurrences (all) Punctate keratitis subjects affected / exposed occurrences (all) Eye pain subjects affected / exposed occurrences (all) Vitreous detachment	13 / 110 (11.82%) 37 4 / 110 (3.64%) 4 4 / 110 (3.64%) 4 8 / 110 (7.27%) 9 3 / 110 (2.73%) 7 		

subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	8		
Cataract			
subjects affected / exposed	6 / 110 (5.45%)		
occurrences (all)	8		
Visual acuity reduced			
subjects affected / exposed	8 / 110 (7.27%)		
occurrences (all)	9		
Conjunctival oedema			
subjects affected / exposed	4 / 110 (3.64%)		
occurrences (all)	17		
Choroidal neovascularisation			
subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	3		
Eye irritation			
subjects affected / exposed	5 / 110 (4.55%)		
occurrences (all)	6		
Posterior capsule opacification			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 110 (0.00%)		
occurrences (all)	0		
Spinal column stenosis			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	10 / 110 (9.09%)		
occurrences (all)	12		
Nasopharyngitis			
subjects affected / exposed	5 / 110 (4.55%)		
occurrences (all)	6		
Sinusitis			

subjects affected / exposed	3 / 110 (2.73%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Influenza			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 110 (1.82%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 March 2016	Amendment A contained clarifications on assessments and inclusion/exclusion criteria.
16 October 2017	Amendment B added Part 2 including a 4 mg dose, updated primary endpoint and inclusion/exclusion criteria.
18 March 2018	Amendment C included minor clarifications and administrative items, and added language that no new patients were to be enrolled in Part 1 after Amendment C.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported