



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 |
|-----------------------|---------|

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) |
|------------------|--|

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) |
|------------------|----------------------|

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 |
|-------|---|---|---|

| 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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Zimura 1 mg |
|-----------------------|-------------|

Reporting group description: -

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

Reporting group description: -

| | |
|-----------------------|-------------|
| Reporting group title | Zimura 4 mg |
|-----------------------|-------------|

Reporting group description: -

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

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