



## Clinical trial results:

### A PHASE 2, RANDOMISED, DOUBLE-MASKED, SHAM-CONTROLLED, MULTI-CENTRE STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OCRIPLASMIN IN INDUCING TOTAL POSTERIOR VITREOUS DETACHMENT (PVD) IN SUBJECTS WITH NON-PROLIFERATIVE DIABETIC RETINOPATHY (NPDR) (CIRCLE)

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2015-002415-15          |
| Trial protocol           | DE GB CZ BE HU ES FR IT |
| Global end of trial date | 18 November 2019        |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 30 November 2020 |
| First version publication date | 30 November 2020 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | TG-MV-015 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02681809 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | ThromboGenics  |
| Sponsor organisation address | Gaston Geenslaan 1, Leuven, Belgium, B-3001                                  |
| Public contact               | Global Clinical Development, ThromboGenics, 32 (0)16751310, info@oxurion.com |
| Scientific contact           | Global Clinical Development, ThromboGenics, 32 (0)16751310, info@oxurion.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                       | 13 January 2020  |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 18 November 2019 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 18 November 2019 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy and safety of up to 3 intravitreal injections of ocriplasmin (0.0625mg or 0.125mg), in subjects with moderate to very severe NPDR, to induce total PVD in order to reduce the risk of disease progression to PDR

Protection of trial subjects:

All study procedures, including the intravitreal injections, were performed by qualified and trained personnel. Only eligible subjects were randomised and only subjects who did not meet any withdrawal criteria received repeat injections. All subjects were supervised in the immediate post-injection period with appropriate medical treatment readily available. Subjects were followed up for 24 months after the first injection. Adverse events were recorded throughout the study period. At each study visit, a full ophthalmic examination and BCVA assessment were performed. An independent DMC was established to maintain a general safety oversight and to monitor the benefit / risk balance for the subjects in the study.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 22 December 2015 |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 22 Months        |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 8  |
| Country: Number of subjects enrolled | Spain: 6           |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | France: 2          |
| Country: Number of subjects enrolled | Hungary: 2         |
| Country: Number of subjects enrolled | Israel: 1          |
| Country: Number of subjects enrolled | United States: 15  |
| Worldwide total number of subjects   | 48                 |
| EEA total number of subjects         | 32                 |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| 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)                      | 32 |
| From 65 to 84 years                       | 16 |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

The study included a Screening visit during which in- and exclusion criteria were checked by the Investigator. In addition, specific criteria needed to be confirmed by the central reading center / by the central laboratory

### Period 1

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

Blinding implementation details:

IMP handling and administration was done by unmasked personnel

### Arms

|                              |                      |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes                  |
| <b>Arm title</b>             | ocriplasmin 0.0625mg |

Arm description: -

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | ocriplasmin 0.5 mg/0.2 mL concentrate for solution for injection |
| Investigational medicinal product code |  |
| Other name                             | JETREA 0.5 mg/0.2 mL concentrate for solution for injection      |
| Pharmaceutical forms                   | Concentrate for solution for injection                           |
| Routes of administration               | Intravitreal use   |

Dosage and administration details:

up to 3 intravitreal injections with ocriplasmin 0.0625mg, approximately 1 month apart

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | ocriplasmin 0.125mg |
|------------------|---------------------|

Arm description: -

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | ocriplasmin 0.5 mg/0.2 mL concentrate for solution for injection |
| Investigational medicinal product code |  |
| Other name                             | JETREA 0.5 mg/0.2 mL concentrate for solution for injection      |
| Pharmaceutical forms                   | Concentrate for solution for injection                           |
| Routes of administration               | Intravitreal use   |

Dosage and administration details:

up to 3 intravitreal injections with ocriplasmin 0.125mg, approximately 1 month apart

|                  |      |
|------------------|------|
| <b>Arm title</b> | sham |
|------------------|------|

Arm description:

Subjects in this arm received a sham injection. There was no penetration of the globe; Investigator mimicked intravitreal injection procedure.

|   |                |
|---|----------------|
| Arm type  | sham injection |
| No investigational medicinal product assigned in this arm |                |

| <b>Number of subjects in period 1</b> | ocriplasmin<br>0.0625mg | ocriplasmin 0.125mg | sham |
|---------------------------------------|-------------------------|---------------------|------|
| Started                               | 20                      | 19                  | 9    |
| Completed                             | 15                      | 15                  | 8    |
| Not completed                         | 5                       | 4                   | 1    |
| Consent withdrawn by subject          | 3                       | 1                   | -    |
| Adverse event, non-fatal              | -                       | 1                   | 1    |
| Lost to follow-up                     | 2                       | 2                   | -    |

## Baseline characteristics

### Reporting groups

|  |                      |
|--|----------------------|
| Reporting group title  | ocriplasmin 0.0625mg |
| Reporting group description: -   |                      |
| Reporting group title  | ocriplasmin 0.125mg  |
| Reporting group description: -   |                      |
| Reporting group title  | sham                 |
| Reporting group description:   |                      |
| Subjects in this arm received a sham injection. There was no penetration of the globe; Investigator mimicked intravitreal injection procedure. |                      |

| Reporting group values                | ocriplasmin<br>0.0625mg | ocriplasmin 0.125mg | sham    |
|---------------------------------------|-------------------------|---------------------|---------|
| Number of subjects                    | 20                      | 19                  | 9       |
| Age categorical<br>Units: Subjects    |                         |                     |         |
| Adults (18-64 years)                  | 12                      | 14                  | 6       |
| From 65-84 years                      | 8                       | 5                   | 3       |
| Age continuous<br>Units: years        |                         |                     |         |
| arithmetic mean                       | 57.7                    | 55.4                | 54.3    |
| standard deviation                    | ± 12.14                 | ± 10.15             | ± 13.01 |
| Gender categorical<br>Units: Subjects |                         |                     |         |
| Female                                | 6                       | 5                   | 2       |
| Male                                  | 14                      | 14                  | 7       |

| Reporting group values                | Total |  |  |
|---------------------------------------|-------|--|--|
| Number of subjects                    | 48    |  |  |
| Age categorical<br>Units: Subjects    |       |  |  |
| Adults (18-64 years)                  | 32    |  |  |
| From 65-84 years                      | 16    |  |  |
| Age continuous<br>Units: years        |       |  |  |
| arithmetic mean                       |       |  |  |
| standard deviation                    | -     |  |  |
| Gender categorical<br>Units: Subjects |       |  |  |
| Female                                | 13    |  |  |
| Male                                  | 35    |  |  |

## End points

### End points reporting groups

|  |                      |
|--|----------------------|
| Reporting group title  | ocriplasmin 0.0625mg |
| Reporting group description: -   |                      |
| Reporting group title  | ocriplasmin 0.125mg  |
| Reporting group description: -   |                      |
| Reporting group title  | sham                 |
| Reporting group description:   |                      |
| Subjects in this arm received a sham injection. There was no penetration of the globe; Investigator mimicked intravitreal injection procedure. |                      |

### Primary: Total PVD by the Month 3 visit, confirmed on both B-scan ultrasound and SD-OCT (6mm), as assessed by the masked B-scan expert reader and the masked CRC, respectively

|                        |  |
|------------------------|--|
| End point title        | Total PVD by the Month 3 visit, confirmed on both B-scan ultrasound and SD-OCT (6mm), as assessed by the masked B-scan expert reader and the masked CRC, respectively <sup>[1]</sup> |
| End point description: |  |
| End point type         | Primary  |
| End point timeframe:   |  |
| at Month 3             |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Recruitment in the study was discontinued early due to slow recruitment rate. This led to a total of 48 randomized subjects instead of the planned 115 per protocol amendment 2. By consequence, the study was not powered for its primary endpoint. The endpoint was therefore evaluated only descriptively. No statistical hypothesis testing was performed.

| End point values            | ocriplasmin<br>0.0625mg | ocriplasmin<br>0.125mg | sham            |  |
|-----------------------------|-------------------------|------------------------|-----------------|--|
| Subject group type          | Reporting group         | Reporting group        | Reporting group |  |
| Number of subjects analysed | 20                      | 18                     | 8               |  |
| Units: subjects             | 0                       | 0                      | 0               |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Ocular treatment-emergent adverse events in the study eye

|  |   |
|--|---|
| End point title  | Ocular treatment-emergent adverse events in the study eye |
| End point description:   |   |
| Incidence of ocular treatment-emergent adverse events in the study eye |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| From first injection until the end of the study (Month 24)             |   |

| <b>End point values</b>     | ocriplasmin<br>0.0625mg | ocriplasmin<br>0.125mg | sham            |  |
|-----------------------------|-------------------------|------------------------|-----------------|--|
| Subject group type          | Reporting group         | Reporting group        | Reporting group |  |
| Number of subjects analysed | 20                      | 19                     | 9               |  |
| Units: subjects             | 15                      | 14                     | 4               |  |

### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first injection until the end of the study (Month 24)

Adverse event reporting additional description:

Adverse events include non-ocular and ocular events (both in study eye and non-study eye)

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

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

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | ocriplasmin 0.0625mg |
|-----------------------|----------------------|

Reporting group description: -

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | ocriplasmin 0.125mg |
|-----------------------|---------------------|

Reporting group description: -

|                       |      |
|-----------------------|------|
| Reporting group title | sham |
|-----------------------|------|

Reporting group description:

Subjects in this arm received a sham injection. There was no penetration of the globe; Investigator to mimic intravitreal injection procedure.

| Serious adverse events  | ocriplasmin<br>0.0625mg | ocriplasmin 0.125mg | sham           |
|---|-------------------------|---------------------|----------------|
| Total subjects affected by serious adverse events                   |                         |                     |                |
| subjects affected / exposed   | 5 / 20 (25.00%)         | 8 / 19 (42.11%)     | 1 / 9 (11.11%) |
| number of deaths (all causes)                                       | 0                       | 0                   | 0              |
| number of deaths resulting from adverse events                      | 0                       | 0                   | 0              |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                     |                |
| Adenocarcinoma of Colon   |                         |                     |                |
| subjects affected / exposed   | 0 / 20 (0.00%)          | 1 / 19 (5.26%)      | 0 / 9 (0.00%)  |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 1               | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0               | 0 / 0          |
| Injury, poisoning and procedural complications                      |                         |                     |                |
| Craniocerebral Injury   |                         |                     |                |
| subjects affected / exposed   | 0 / 20 (0.00%)          | 0 / 19 (0.00%)      | 1 / 9 (11.11%) |
| occurrences causally related to treatment / all                     | 0 / 0                   | 0 / 0               | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0               | 0 / 0          |
| Fibula Fracture   |                         |                     |                |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Patella Fracture                                |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Pelvic Fracture                                 |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Vascular disorders                              |                |                |               |
| Peripheral Ischaemia                            |                |                |               |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (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 disorders                               |                |                |               |
| Cardiac Failure                                 |                |                |               |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 1 / 19 (5.26%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Cardiac Failure Congestive                      |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Nervous system disorders                        |                |                |               |
| Cerebrovascular Accident                        |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Blood and lymphatic system disorders            |                |                |               |
| Anaemia   |                |                |               |

|  |                |                |               |
|--|----------------|----------------|---------------|
| subjects affected / exposed                          | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| General disorders and administration site conditions |                |                |               |
| Generalised Oedema                                   |                |                |               |
| subjects affected / exposed                          | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (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         |
| Non-Cardiac Chest Pain                               |                |                |               |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Eye disorders  |                |                |               |
| Ciliary Zonular Dehiscence                           |                |                |               |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Retinal Haemorrhage                                  |                |                |               |
| subjects affected / exposed                          | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (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         |
| Uveitis  |                |                |               |
| subjects affected / exposed                          | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0         |
| Gastrointestinal disorders                           |                |                |               |
| Constipation   |                |                |               |
| subjects affected / exposed                          | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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      |                |                |               |
| Acute Respiratory Failure                            |                |                |               |

|   |                |                |               |
|---|----------------|----------------|---------------|
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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 Failure                             |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Musculoskeletal and connective tissue disorders |                |                |               |
| Myalgia   |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Infections and infestations                     |                |                |               |
| Respiratory Tract Infection                     |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |
| Abdominal Wall Abscess                          |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Catheter Site Cellulitis                        |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Cellulitis                                      |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |
| Endophthalmitis                                 |                |                |               |
| subjects affected / exposed                     | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0         |

|   |                |                |               |
|---|----------------|----------------|---------------|
| Pneumonia                                       |                |                |               |
| subjects affected / exposed                     | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (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         |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                           | ocriplasmin<br>0.0625mg | ocriplasmin 0.125mg | sham           |
|---|-------------------------|---------------------|----------------|
| Total subjects affected by non-serious adverse events       |                         |                     |                |
| subjects affected / exposed                                 | 16 / 20 (80.00%)        | 17 / 19 (89.47%)    | 7 / 9 (77.78%) |
| <b>Vascular disorders</b>                                   |                         |                     |                |
| Hypertension  |                         |                     |                |
| subjects affected / exposed                                 | 1 / 20 (5.00%)          | 2 / 19 (10.53%)     | 1 / 9 (11.11%) |
| occurrences (all)   | 1                       | 3                   | 1              |
| Deep Vein Thrombosis  |                         |                     |                |
| subjects affected / exposed                                 | 0 / 20 (0.00%)          | 1 / 19 (5.26%)      | 0 / 9 (0.00%)  |
| occurrences (all)   | 0                       | 1                   | 0              |
| Hypertensive Crisis   |                         |                     |                |
| subjects affected / exposed                                 | 0 / 20 (0.00%)          | 1 / 19 (5.26%)      | 0 / 9 (0.00%)  |
| occurrences (all)   | 0                       | 1                   | 0              |
| Peripheral Ischaemia  |                         |                     |                |
| subjects affected / exposed                                 | 1 / 20 (5.00%)          | 0 / 19 (0.00%)      | 0 / 9 (0.00%)  |
| occurrences (all)   | 2                       | 0                   | 0              |
| <b>General disorders and administration site conditions</b> |                         |                     |                |
| Malaise   |                         |                     |                |
| subjects affected / exposed                                 | 0 / 20 (0.00%)          | 0 / 19 (0.00%)      | 1 / 9 (11.11%) |
| occurrences (all)   | 0                       | 0                   | 2              |
| Gait Disturbance  |                         |                     |                |
| subjects affected / exposed                                 | 1 / 20 (5.00%)          | 0 / 19 (0.00%)      | 0 / 9 (0.00%)  |
| occurrences (all)   | 1                       | 0                   | 0              |
| Injection Site Haemorrhage                                  |                         |                     |                |
| subjects affected / exposed                                 | 1 / 20 (5.00%)          | 0 / 19 (0.00%)      | 0 / 9 (0.00%)  |
| occurrences (all)   | 1                       | 0                   | 0              |
| Injection Site Pain   |                         |                     |                |

|   |                      |                      |                     |
|---|----------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 0 / 19 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)          | 0 / 20 (0.00%)<br>0  | 1 / 19 (5.26%)<br>1  | 0 / 9 (0.00%)<br>0  |
| Pulmonary Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0  | 0 / 19 (0.00%)<br>0  | 1 / 9 (11.11%)<br>1 |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 20 (0.00%)<br>0  | 1 / 19 (5.26%)<br>1  | 0 / 9 (0.00%)<br>0  |
| Investigations<br>Intraocular Pressure Increased<br>subjects affected / exposed<br>occurrences (all)                  | 4 / 20 (20.00%)<br>6 | 0 / 19 (0.00%)<br>0  | 1 / 9 (11.11%)<br>2 |
| Glycosylated Haemoglobin Increased<br>subjects affected / exposed<br>occurrences (all)                                | 0 / 20 (0.00%)<br>0  | 3 / 19 (15.79%)<br>3 | 0 / 9 (0.00%)<br>0  |
| Intraocular Pressure Decreased<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 20 (5.00%)<br>1  | 0 / 19 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0  |
| Injury, poisoning and procedural complications<br>Pelvic Fracture<br>subjects affected / exposed<br>occurrences (all) | 0 / 20 (0.00%)<br>0  | 1 / 19 (5.26%)<br>1  | 0 / 9 (0.00%)<br>0  |
| Post Procedural Oedema<br>subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0  | 1 / 19 (5.26%)<br>1  | 0 / 9 (0.00%)<br>0  |
| Radius Fracture<br>subjects affected / exposed<br>occurrences (all)   | 0 / 20 (0.00%)<br>0  | 1 / 19 (5.26%)<br>1  | 0 / 9 (0.00%)<br>0  |
| Congenital, familial and genetic disorders  |                      |                      |                     |

|   |  |   |   |
|---|--|---|---|
| Colour Blindness<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 0 / 19 (0.00%)<br>0   | 0 / 9 (0.00%)<br>0  |
| Cardiac disorders<br>Cardiac Failure<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1  | 1 / 19 (5.26%)<br>1   | 0 / 9 (0.00%)<br>0  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Loss of Consciousness<br>subjects affected / exposed<br>occurrences (all)<br><br>Paralysis<br>subjects affected / exposed<br>occurrences (all)<br><br>Sciatica<br>subjects affected / exposed<br>occurrences (all) | 2 / 20 (10.00%)<br>2<br><br>0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0<br><br>1 / 20 (5.00%)<br>1<br><br>0 / 20 (0.00%)<br>0 | 2 / 19 (10.53%)<br>2<br><br>0 / 19 (0.00%)<br>0<br><br>0 / 19 (0.00%)<br>0<br><br>0 / 19 (0.00%)<br>0 | 0 / 9 (0.00%)<br>0<br><br>1 / 9 (11.11%)<br>1<br><br>1 / 9 (11.11%)<br>1<br><br>0 / 9 (0.00%)<br>0<br><br>1 / 9 (11.11%)<br>1 |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)  | 0 / 20 (0.00%)<br>0  | 1 / 19 (5.26%)<br>1   | 0 / 9 (0.00%)<br>0  |
| Eye disorders<br>Eye Pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Diabetic Retinal Oedema<br>subjects affected / exposed<br>occurrences (all)<br><br>Cataract<br>subjects affected / exposed<br>occurrences (all)  | 2 / 20 (10.00%)<br>2<br><br>4 / 20 (20.00%)<br>4<br><br>3 / 20 (15.00%)<br>4   | 5 / 19 (26.32%)<br>7<br><br>1 / 19 (5.26%)<br>3<br><br>3 / 19 (15.79%)<br>4                           | 1 / 9 (11.11%)<br>1<br><br>2 / 9 (22.22%)<br>3<br><br>0 / 9 (0.00%)<br>0  |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| Visual Acuity Reduced       |                 |                 |                |
| subjects affected / exposed | 2 / 20 (10.00%) | 4 / 19 (21.05%) | 0 / 9 (0.00%)  |
| occurrences (all)           | 2               | 4               | 0              |
| Vitreous Floaters           |                 |                 |                |
| subjects affected / exposed | 2 / 20 (10.00%) | 3 / 19 (15.79%) | 0 / 9 (0.00%)  |
| occurrences (all)           | 2               | 6               | 0              |
| Conjunctival Haemorrhage    |                 |                 |                |
| subjects affected / exposed | 4 / 20 (20.00%) | 1 / 19 (5.26%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 4               | 1               | 0              |
| Macular Oedema              |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 4 / 19 (21.05%) | 0 / 9 (0.00%)  |
| occurrences (all)           | 0               | 5               | 0              |
| Visual Impairment           |                 |                 |                |
| subjects affected / exposed | 3 / 20 (15.00%) | 1 / 19 (5.26%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 4               | 1               | 0              |
| Vitreous Haemorrhage        |                 |                 |                |
| subjects affected / exposed | 1 / 20 (5.00%)  | 3 / 19 (15.79%) | 0 / 9 (0.00%)  |
| occurrences (all)           | 2               | 3               | 0              |
| Photophobia                 |                 |                 |                |
| subjects affected / exposed | 1 / 20 (5.00%)  | 2 / 19 (10.53%) | 0 / 9 (0.00%)  |
| occurrences (all)           | 1               | 4               | 0              |
| Photopsia                   |                 |                 |                |
| subjects affected / exposed | 1 / 20 (5.00%)  | 2 / 19 (10.53%) | 0 / 9 (0.00%)  |
| occurrences (all)           | 1               | 4               | 0              |
| Diabetic Retinopathy        |                 |                 |                |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 19 (0.00%)  | 2 / 9 (22.22%) |
| occurrences (all)           | 2               | 0               | 2              |
| Dry Eye                     |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 2 / 19 (10.53%) | 1 / 9 (11.11%) |
| occurrences (all)           | 0               | 3               | 1              |
| Eye Irritation              |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 2 / 19 (10.53%) | 1 / 9 (11.11%) |
| occurrences (all)           | 0               | 3               | 1              |
| Macular Fibrosis            |                 |                 |                |
| subjects affected / exposed | 2 / 20 (10.00%) | 1 / 19 (5.26%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 3               | 1               | 0              |



|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| Retinal Haemorrhage         |                 |                 |                |
| subjects affected / exposed | 2 / 20 (10.00%) | 1 / 19 (5.26%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 2               | 1               | 0              |
| Vision Blurred              |                 |                 |                |
| subjects affected / exposed | 1 / 20 (5.00%)  | 1 / 19 (5.26%)  | 1 / 9 (11.11%) |
| occurrences (all)           | 1               | 1               | 1              |
| Cataract Subcapsular        |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 2 / 19 (10.53%) | 0 / 9 (0.00%)  |
| occurrences (all)           | 0               | 3               | 0              |
| Lacrimation Increased       |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 2 / 19 (10.53%) | 0 / 9 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0              |
| Punctate Keratitis          |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 1 / 19 (5.26%)  | 1 / 9 (11.11%) |
| occurrences (all)           | 0               | 1               | 1              |
| Cataract Cortical           |                 |                 |                |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 19 (0.00%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0              |
| Iridocyclitis               |                 |                 |                |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 19 (0.00%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0              |
| Lenticular Opacities        |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 1 / 19 (5.26%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0              |
| Ocular Hypertension         |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 1 / 19 (5.26%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 0               | 2               | 0              |
| Cataract Nuclear            |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 1 / 19 (5.26%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0              |
| Corneal Oedema              |                 |                 |                |
| subjects affected / exposed | 1 / 20 (5.00%)  | 0 / 19 (0.00%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0              |
| Cystoid Macular Oedema      |                 |                 |                |
| subjects affected / exposed | 0 / 20 (0.00%)  | 1 / 19 (5.26%)  | 0 / 9 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0              |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Eyelid Ptosis                             |                |                |                |
| subjects affected / exposed               | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 1              | 0              | 0              |
| Ocular Hyperaemia                         |                |                |                |
| subjects affected / exposed               | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 1              | 0              | 0              |
| Optic Disc Haemorrhage                    |                |                |                |
| subjects affected / exposed               | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 0              | 1              | 0              |
| Optic Nerve Disorder                      |                |                |                |
| subjects affected / exposed               | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 1              | 0              | 0              |
| Retinal Aneurysm                          |                |                |                |
| subjects affected / exposed               | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 1              | 0              | 0              |
| Retinal Cyst                              |                |                |                |
| subjects affected / exposed               | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 1              | 0              | 0              |
| Retinal Detachment                        |                |                |                |
| subjects affected / exposed               | 0 / 20 (0.00%) | 0 / 19 (0.00%) | 1 / 9 (11.11%) |
| occurrences (all)                         | 0              | 0              | 1              |
| Retinal Exudates                          |                |                |                |
| subjects affected / exposed               | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 1              | 0              | 0              |
| Gastrointestinal disorders                |                |                |                |
| Constipation                              |                |                |                |
| subjects affected / exposed               | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 0              | 1              | 0              |
| Diarrhoea                                 |                |                |                |
| subjects affected / exposed               | 0 / 20 (0.00%) | 1 / 19 (5.26%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 0              | 1              | 0              |
| Gastrooesophageal Sphincter Insufficiency |                |                |                |
| subjects affected / exposed               | 1 / 20 (5.00%) | 0 / 19 (0.00%) | 0 / 9 (0.00%)  |
| occurrences (all)                         | 1              | 0              | 0              |
| Skin and subcutaneous tissue disorders    |                |                |                |

|   |   |  |  |
|---|---|--|--|
| Dermatitis Herpetiformis<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>1   | 0 / 19 (0.00%)<br>0  | 0 / 9 (0.00%)<br>0   |
| Renal and urinary disorders<br>Renal Failure<br>subjects affected / exposed<br>occurrences (all)  | 1 / 20 (5.00%)<br>2   | 1 / 19 (5.26%)<br>1  | 1 / 9 (11.11%)<br>1  |
| Musculoskeletal and connective tissue disorders<br>Joint Swelling<br>subjects affected / exposed<br>occurrences (all)<br><br>Musculoskeletal Chest Pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0                             | 1 / 19 (5.26%)<br>1<br><br>1 / 19 (5.26%)<br>1<br><br>0 / 19 (0.00%)<br>0                              | 0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0<br><br>1 / 9 (11.11%)<br>1                            |
| Infections and infestations<br>Viral Upper Respiratory Tract Infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Cellulitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Localised Infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Nosocomial Infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 20 (10.00%)<br>2<br><br>1 / 20 (5.00%)<br>1<br><br>0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0 | 3 / 19 (15.79%)<br>3<br><br>0 / 19 (0.00%)<br>0<br><br>2 / 19 (10.53%)<br>2<br><br>0 / 19 (0.00%)<br>0 | 2 / 9 (22.22%)<br>2<br><br>0 / 9 (0.00%)<br>0<br><br>0 / 9 (0.00%)<br>0<br><br>1 / 9 (11.11%)<br>1 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 28 October 2016 | Sample size was reduced and eligibility criteria were updated to improve recruitment |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Recruitment in the study was discontinued early due to slow recruitment rate. This led to a total of 48 randomized subjects instead of the planned 115 per protocol amendment 2. By consequence, the study was not powered for its primary endpoint.

Notes: