



## Clinical trial results:

### Assessment of Anatomical and Functional Outcomes in Patients Treated with Ocriplasmin for Vitreomacular Traction/Symptomatic Vitreomacular Adhesion (VMT/sVMA)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2013-005464-25                |
| Trial protocol           | HU GB DE IT ES NL PT BE PL FR |
| Global end of trial date | 02 September 2015             |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 30 August 2016 |
| First version publication date | 30 August 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | M-13-056 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02035748 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Alcon, A Novartis Division   |
| Sponsor organisation address | 6201 S. Freeway, Fort Worth, Texas, United States, 76134   |
| Public contact               | EMA Medical Affairs Lead, Pharma, Alcon, A Novartis Division, +1 888-451-3937, alcon.medinfo@alcon.com |
| Scientific contact           | EMA Medical Affairs Lead, Pharma, Alcon, A Novartis Division, +1 888-451-3937, alcon.medinfo@alcon.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                       | 02 September 2015 |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 02 September 2015 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to observe the anatomical and functional outcomes of ocriplasmin (JETREA®) over a 6-month follow-up period. After receiving a single intravitreal injection as per country's product label (Day 0), subjects were followed for a 6-month period (Day 180).

Protection of trial subjects:

This study was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP), including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 21 April 2014 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 35    |
| Country: Number of subjects enrolled | Poland: 30         |
| Country: Number of subjects enrolled | Portugal: 9        |
| Country: Number of subjects enrolled | Spain: 34          |
| Country: Number of subjects enrolled | United Kingdom: 60 |
| Country: Number of subjects enrolled | Belgium: 40        |
| Country: Number of subjects enrolled | France: 99         |
| Country: Number of subjects enrolled | Germany: 33        |
| Country: Number of subjects enrolled | Hungary: 23        |
| Country: Number of subjects enrolled | Italy: 38          |
| Country: Number of subjects enrolled | Canada: 67         |
| Worldwide total number of subjects   | 468                |
| EEA total number of subjects         | 401                |

Notes:

### Subjects enrolled per age group

|  |   |
|--|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|  |     |
|--|-----|
| wk                                       |     |
| 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)                     | 81  |
| From 65 to 84 years                      | 364 |
| 85 years and over                        | 23  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited from 87 study centers located in Europe and Canada (10 Italy, 5 Netherlands, 4 Poland, 4 Portugal, 12 Spain, 15 United Kingdom, 3 Belgium, 12 France, 9 Germany, 5 Hungary, and 8 Canada).

### Pre-assignment

Screening details:

Of the 628 enrolled, 160 subjects were exited prior to initiation of treatment. This reporting group includes all treated subjects (468).

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|           |             |
|-----------|-------------|
| Arm title | Ocriplasmin |
|-----------|-------------|

Arm description:

Ocriplasmin 0.125 mg in a 0.1 mL volume administered as a single dose by intravitreal injection

|  |  |
|--|--|
| Arm type                               | Experimental                           |
| Investigational medicinal product name | Ocriplasmin                            |
| Investigational medicinal product code |  |
| Other name                             | JETREA                                 |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intravitreal use                       |

Dosage and administration details:

0.5 mg/0.2 mL solution for injection

| Number of subjects in period 1 | Ocriplasmin |
|--------------------------------|-------------|
| Started                        | 468         |
| Full Analysis Set              | 466         |
| Completed                      | 448         |
| Not completed                  | 20          |
| Physician decision             | 3           |
| Adverse event, non-fatal       | 5           |
| Death                          | 3           |
| Progressive disease            | 1           |
| Lost to follow-up              | 2           |
| Withdrawal by subject          | 6           |



## Baseline characteristics

### Reporting groups

|   |               |
|---|---------------|
| Reporting group title   | Overall study |
| Reporting group description:  |               |
| Ocriplasmin 0.125 mg in a 0.1 mL volume administered as a single dose by intravitreal injection |               |

| Reporting group values | Overall study | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 468           | 468   |  |
| Age categorical        |               |       |  |
| Units: Subjects        |               |       |  |
| Age continuous         |               |       |  |
| Units: years           |               |       |  |
| arithmetic mean        | 71.7          |       |  |
| standard deviation     | ± 8.3         | -     |  |
| Gender categorical     |               |       |  |
| Units: Subjects        |               |       |  |
| Female                 | 345           | 345   |  |
| Male                   | 123           | 123   |  |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Ocriplasmin |
| Reporting group description:  |             |
| Ocriplasmin 0.125 mg in a 0.1 mL volume administered as a single dose by intravitreal injection |             |

### Primary: Proportion of Subjects With Nonsurgical Resolution of Focal Vitreomacular Traction (VMT/VMA) at Day 28, as Determined by Central Reading Center (CRC) Spectral Domain Optical Coherence Tomography (SD-OCT) Evaluation

|                 |   |
|-----------------|---|
| End point title | Proportion of Subjects With Nonsurgical Resolution of Focal Vitreomacular Traction (VMT/VMA) at Day 28, as Determined by Central Reading Center (CRC) Spectral Domain Optical Coherence Tomography (SD-OCT) Evaluation <sup>[1]</sup> |
|-----------------|---|

#### End point description:

Vitreous separation was assessed by SD-OCT using scores ranging from 1 (vitreous attached from macula to ON; separated elsewhere cannot determine foveal) to 12 (unable to determine state of separation). Nonsurgical resolution was defined as a change from baseline score of 5/6/8 to 7/9/10 at Day 28. The assessment of resolution of VMT/sVMA was based upon the anatomical resolution of VMA only, i.e. no resolution of the related symptoms was considered. Thus, the term VMA is used interchangeably with VMT/sVMA. Proportion of subjects is presented as a percentage, with percentage based on the number of subjects who have VMT/sVMA at baseline and SD-OCT value at Day 28. One eye (study eye) contributed to the analysis.

Subjects treated with IP with at least one post-treatment SD-OCT measurement (FAS). Missing data imputed using the last observation carried forward (LOCF) method. Subjects with vitrectomy after VMT/sVMA resolution were considered 'no resolution' after timepoint of vitrectomy.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Baseline, Day 28     |         |

#### 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: No statistical analysis was performed

| End point values              | Ocriplasmin     |  |  |  |
|-------------------------------|-----------------|--|--|--|
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 466             |  |  |  |
| Units: percentage of subjects |                 |  |  |  |
| number (not applicable)       | 47.4            |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Nonsurgical Change From Baseline in Best-corrected Visual Acuity (BCVA) at Distance

|                 |   |
|-----------------|---|
| End point title | Nonsurgical Change From Baseline in Best-corrected Visual Acuity (BCVA) at Distance |
|-----------------|---|

End point description:

BCVA (with spectacles or other visual corrective devices) was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) testing at 4 meters. The charts contain 14 rows of letters. BCVA was calculated as the number of letters read correctly and improvement defined as an increase (gain) in letters read from the baseline assessment. One eye (study eye) contributed to the analysis.

Full Analysis Set. Missing data imputed using LOCF. BCVA values after a vitrectomy were imputed with the last non-missing value prior to the vitrectomy.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 0), Day 28, Day 90, Day 180

| End point values                     | Ocriplasmin     |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 448             |  |  |  |
| Units: letters                       |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Change from baseline at Day 28       | 1.7 (± 6.7)     |  |  |  |
| Change from baseline at Day 90       | 3 (± 7.07)      |  |  |  |
| Change from baseline at Day 180      | 3.5 (± 7.77)    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects With Nonsurgical Closure of Macular Hole (MH), if Present at Baseline

|                 |  |
|-----------------|--|
| End point title | Proportion of Subjects With Nonsurgical Closure of Macular Hole (MH), if Present at Baseline |
|-----------------|--|

End point description:

The closure of macular hole (a full thickness defect of the retinal tissue involving the anatomical fovea) is defined as a flattened and reattached hole rim along the whole circumference of macular hole. Closure was determined by SD-OCT evaluation and the percentage of subjects tabulated. Proportion of subjects is presented as a percentage, with percentage based on the number of subjects who had macular hole at baseline and OCT value at each specific visit. One eye (study eye) contributed to the analysis.

Full Analysis Set. Missing data imputed using LOCF. Subjects who had vitrectomy after MH closure were considered as 'no MH closure' after the timepoint of vitrectomy.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 28, Day 90, Day 180



| End point values              | Ocriplasmin     |  |  |  |
|-------------------------------|-----------------|--|--|--|
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 86              |  |  |  |
| Units: percentage of subjects |                 |  |  |  |
| number (not applicable)       |                 |  |  |  |
| Day 28                        | 39.5            |  |  |  |
| Day 90                        | 40.7            |  |  |  |
| Day 180                       | 41.9            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects With Nonsurgical Resolution of VMT/sVMA

|                 |  |
|-----------------|--|
| End point title | Proportion of Subjects With Nonsurgical Resolution of VMT/sVMA |
|-----------------|--|

End point description:

Vitreous separation was assessed by SD-OCT using scores ranging from 1 (vitreous attached from macula to ON; separated elsewhere cannot determine foveal) to 12 (unable to determine state of separation). Nonsurgical resolution was defined as a change from baseline score of 5/6/8 to 7/9/10 at Day 90 and Day 180. The assessment of resolution of VMT/sVMA was based upon the anatomical resolution of VMA only, i.e. no resolution of the related symptoms was considered. Thus, the term VMA is used interchangeably with VMT/sVMA. Proportion of subjects is presented as a percentage, with percentage based on the number of subjects who have VMT/sVMA at baseline and SD-OCT value at Day 90/Day 180. One eye (study eye) contributed to the analysis.

Full Analysis Set. Missing data imputed using LOCF. Subjects who had vitrectomy after VMT/sVMA resolution were considered as 'no resolution' after the timepoint of vitrectomy.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 90, Day 180

| End point values              | Ocriplasmin     |  |  |  |
|-------------------------------|-----------------|--|--|--|
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 466             |  |  |  |
| Units: percentage of subjects |                 |  |  |  |
| number (not applicable)       |                 |  |  |  |
| Day 90                        | 47.9            |  |  |  |
| Day 180                       | 49.4            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of Subjects Experiencing Pars Plana Vitrectomy (PPV) at Day 180

|   |  |
|---|--|
| End point title   | Proportion of Subjects Experiencing Pars Plana Vitrectomy (PPV) at Day 180 |
| End point description:<br>Pars plana vitrectomy (the surgical removal of vitreous gel from the eye) was captured in Concomitant Ocular Procedures. Proportion of subjects is reported as a percentage. One eye (study eye) contributed to the analysis. |  |
| Full Analysis Set   |  |
| End point type  | Secondary  |
| End point timeframe:<br>Day 180   |  |

|                               |                 |  |  |  |
|-------------------------------|-----------------|--|--|--|
| <b>End point values</b>       | Ocriplasmin     |  |  |  |
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 466             |  |  |  |
| Units: percentage of subjects |                 |  |  |  |
| number (not applicable)       | 12              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Mean Nonsurgical Change From Baseline in Central Foveal Thickness (CFT)

|   |   |
|---|---|
| End point title   | Mean Nonsurgical Change From Baseline in Central Foveal Thickness (CFT) |
| End point description:<br>Nonsurgical change in central foveal thickness (CFT values after a vitrectomy were imputed with the last non-missing value prior to the vitrectomy) was determined by subtracting the measurements in subretinal fluid and retinal pigment epithelium (RPE) elevations and/or SHRM (subretinal hyper-reflective material such as choroidal neovascularization (CNV)) from the value in total retinal measurement. A lower CFT indicates improvement. One eye (study eye) contributed to the analysis. |   |
| Full Analysis Set. Missing data is imputed using LOCF. CFT values after a vitrectomy were imputed with the last non-missing value prior to the vitrectomy.  |   |
| End point type  | Secondary   |
| End point timeframe:<br>Baseline (Day 0), Day 28, Day 180   |   |

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Ocriplasmin     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 466             |  |  |  |
| Units: micrometers                   |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Baseline (Day 0), n=466              | 276.1 (± 166.4) |  |  |  |

|   |                     |  |  |  |
|---|---------------------|--|--|--|
| Change from baseline at Day 28, n=465     | -43.2 (±<br>113.47) |  |  |  |
| Change from baseline at Day 180,<br>n=466 | -45.4 (±<br>131.84) |  |  |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected for the duration of a subject's participation in the study (up to 7 months). Ocular AEs are presented for both study eye and non-study eye combined. AEs are reported as treatment-emergent.

Adverse event reporting additional description:

An AE was defined as any untoward medical occurrence in a subject regardless of the causal relationship to the study medication. AEs could be volunteered or solicited by the Investigator or study personnel.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Ocriplasmin |
|-----------------------|-------------|

Reporting group description:

All subjects exposed to the investigational product

| Serious adverse events  | Ocriplasmin      |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events                   |                  |  |  |
| subjects affected / exposed   | 46 / 468 (9.83%) |  |  |
| number of deaths (all causes)                                       | 4                |  |  |
| number of deaths resulting from adverse events                      | 0                |  |  |
| Investigations  |                  |  |  |
| Colonoscopy   |                  |  |  |
| subjects affected / exposed   | 1 / 468 (0.21%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| Breast cancer   |                  |  |  |
| subjects affected / exposed   | 1 / 468 (0.21%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Breast cancer metastatic  |                  |  |  |
| subjects affected / exposed   | 1 / 468 (0.21%)  |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 1            |  |  |
| Oesophageal carcinoma   |                  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchial carcinoma                             |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Fall  |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femoral neck fracture                           |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Cardiac failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Left ventricular failure                        |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Arrhythmia                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Surgical and medical procedures                 |                 |  |  |
| Cardioversion                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear operation                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Heart valve replacement                         |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hip arthroplasty                                |                 |  |  |
| subjects affected / exposed                     | 2 / 468 (0.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hip surgery                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lithotripsy                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal stone removal                             |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Shoulder operation                              |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vitrectomy                                      |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Nervous system disorders                             |                 |  |  |
| Cerebrovascular accident                             |                 |  |  |
| subjects affected / exposed                          | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Disturbance in attention                             |                 |  |  |
| subjects affected / exposed                          | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Syncope  |                 |  |  |
| subjects affected / exposed                          | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Oedema peripheral                                    |                 |  |  |
| subjects affected / exposed                          | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Eye disorders  |                 |  |  |
| Ciliary zonular dehiscence                           |                 |  |  |
| subjects affected / exposed                          | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Macular hole   |                 |  |  |
| subjects affected / exposed                          | 8 / 468 (1.71%) |  |  |
| occurrences causally related to treatment / all      | 4 / 8           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Retinal detachment                                   |                 |  |  |
| subjects affected / exposed                          | 4 / 468 (0.85%) |  |  |
| occurrences causally related to treatment / all      | 4 / 4           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Visual acuity reduced                           |                 |  |  |
| subjects affected / exposed                     | 5 / 468 (1.07%) |  |  |
| occurrences causally related to treatment / all | 5 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vitreous adhesions                              |                 |  |  |
| subjects affected / exposed                     | 2 / 468 (0.43%) |  |  |
| occurrences causally related to treatment / all | 2 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal obstruction                          |                 |  |  |
| subjects affected / exposed                     | 2 / 468 (0.43%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Rectal prolapse                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Chronic obstructive pulmonary disease           |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pickwickian syndrome                            |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Nephrolithiasis                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Bacterial sepsis                                |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung infection                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sepsis  |                 |  |  |
| subjects affected / exposed                     | 1 / 468 (0.21%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |

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

| <b>Non-serious adverse events</b>                     | Ocriplasmin        |  |  |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 247 / 468 (52.78%) |  |  |
| Eye disorders   |                    |  |  |
| Colour blindness acquired                             |                    |  |  |
| subjects affected / exposed                           | 26 / 468 (5.56%)   |  |  |
| occurrences (all)                                     | 26                 |  |  |
| Eye pain  |                    |  |  |
| subjects affected / exposed                           | 40 / 468 (8.55%)   |  |  |
| occurrences (all)                                     | 41                 |  |  |
| Macular oedema  |                    |  |  |

|                             |                    |  |  |
|-----------------------------|--------------------|--|--|
| subjects affected / exposed | 52 / 468 (11.11%)  |  |  |
| occurrences (all)           | 53                 |  |  |
| Photophobia                 |                    |  |  |
| subjects affected / exposed | 24 / 468 (5.13%)   |  |  |
| occurrences (all)           | 27                 |  |  |
| Photopsia                   |                    |  |  |
| subjects affected / exposed | 104 / 468 (22.22%) |  |  |
| occurrences (all)           | 114                |  |  |
| Vision blurred              |                    |  |  |
| subjects affected / exposed | 54 / 468 (11.54%)  |  |  |
| occurrences (all)           | 62                 |  |  |
| Visual acuity reduced       |                    |  |  |
| subjects affected / exposed | 127 / 468 (27.14%) |  |  |
| occurrences (all)           | 138                |  |  |
| Vitreous floaters           |                    |  |  |
| subjects affected / exposed | 78 / 468 (16.67%)  |  |  |
| occurrences (all)           | 93                 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date          | Amendment  |
|---------------|--|
| 04 March 2014 | The purpose of this amendment was to include additional exclusion criteria to ensure that patients for whom treatment was not recommended were not enrolled in this study. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported