# Clinical trial results:
# A Multicenter, Open-label, Randomized Study Comparing the Efficacy and Safety of 700 g Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) to Ranibizumab in Patients With Diabetic Macular Edema

## Summary

| | |
|---|---|
| EudraCT number | 2011-005631-20 |
| Trial protocol | DE BE PT SE ES GB NL AT DK IT |
| Global end of trial date | 13 February 2014 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 21 April 2016 |
| First version publication date | 21 April 2016 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 206207-024 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01492400 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Allergan Limited |
| Sponsor organisation address | Allergan Limited Marlow International The Parkway, Marlow, United Kingdom, SL7 1YL |
| Public contact | Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com |
| Scientific contact | Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.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 | 21 May 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 13 February 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 13 February 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate whether treatment with 700 µg DEX PS DDS every 5 months provides a similar treatment effect on average change of best-corrected visual acuity (BCVA) as ranibizumab administered as per its European Summary of Product Characteristics (SmPC) in patients with DME

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form .

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 09 March 2012 |
| 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 | United States: 143 |
| Country: Number of subjects enrolled | United Kingdom: 29 |
| Country: Number of subjects enrolled | Denmark: 5 |
| Country: Number of subjects enrolled | Spain: 14 |
| Country: Number of subjects enrolled | France: 33 |
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Israel: 85 |
| Country: Number of subjects enrolled | Italy: 26 |
| Country: Number of subjects enrolled | Netherlands Antilles: 2 |
| Country: Number of subjects enrolled | Portugal: 17 |
| Country: Number of subjects enrolled | South Africa: 2 |
| Worldwide total number of subjects | 363 |
| EEA total number of subjects | 131 |

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) | 187 |
| From 65 to 84 years | 173 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients were screened up to 2 weeks prior to randomization on Day 1.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Assessor[1] |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | dexamethasone Intravitreal Implant |

Arm description:

Injection of 700 ug dexamethasone intravitreal implant into the study eye on Day 1, Month 5, and Month 10.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Implant |
| Routes of administration | Implantation |

Dosage and administration details:

Injection of 700 ug dexamethasone intravitreal implant into the study eye on Day 1, Month 5, and Month 10.

| | |
|---|---|
| **Arm title** | ranibizumab |

Arm description:

Injection of ranibizumab 0.5 mg into the study eye on Day 1. Patients may receive additional injections on a monthly basis, as needed, for disease progression.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | ranibizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

Injection of ranibizumab 0.5 mg into the study eye on Day 1. Patients may receive additional injections on a monthly basis, as needed, for disease progression.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only the Outcome Assessor was blinded for this trial.

| **Number of subjects in period 1** | dexamethasone Intravitreal Implant | ranibizumab |
|---|---|---|
| Started | 181 | 182 |
| Completed | 165 | 166 |
| Not completed | 16 | 16 |
| Adverse event, non-fatal | 10 | 5 |
| Miscellaneous Reasons | 2 | 3 |
| Pregnancy | - | 1 |
| Personal Reasons | - | 5 |
| Lost to follow-up | 3 | 1 |
| Lack of efficacy | 1 | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | dexamethasone Intravitreal Implant |
| Reporting group description: | |
| Injection of 700 ug dexamethasone intravitreal implant into the study eye on Day 1, Month 5, and Month 10. | |
| Reporting group title | ranibizumab |
| Reporting group description: | |
| Injection of ranibizumab 0.5 mg into the study eye on Day 1. Patients may receive additional injections on a monthly basis, as needed, for disease progression. | |

| Reporting group values | dexamethasone Intravitreal Implant | ranibizumab | Total |
|---|---|---|---|
| Number of subjects | 181 | 182 | 363 |
| Age categorical<br>Units: Subjects | | | |
| Adults (18-64 years) | 98 | 89 | 187 |
| From 65-84 years | 81 | 92 | 173 |
| 85 years and over | 2 | 1 | 3 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 63.4 | 63.7 | |
| standard deviation | ± 9.39 | ± 10.05 | - |
| Gender, Male/Female<br>Units: Participants | | | |
| Female | 69 | 66 | 135 |
| Male | 112 | 116 | 228 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | dexamethasone Intravitreal Implant |
| Reporting group description: | |
| Injection of 700 ug dexamethasone intravitreal implant into the study eye on Day 1, Month 5, and Month 10. | |
| Reporting group title | ranibizumab |
| Reporting group description: | |
| Injection of ranibizumab 0.5 mg into the study eye on Day 1. Patients may receive additional injections on a monthly basis, as needed, for disease progression. | |

### Primary: Average Change from Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye

| | |
|---|---|
| End point title | Average Change from Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye[1] |
| End point description: | |
| BCVA is measured using an eye chart and is reported as the number of letters read correctly (ranging from 0 to 100 letters) in the study eye. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). The average BCVA is calculated across study visits for each patient. A positive number change from baseline indicates an improvement and a negative number change from baseline indicates a worsening. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, 12 Months | |

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 is reported for this outcome measure.

| End point values | dexamethasone Intravitreal Implant | ranibizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 181 | 182 | | |
| Units: Letters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 60.2 (± 9.74) | 60.4 (± 9.34) | | |
| Change from Baseline at 12 Months | 4.34 (± 7.342) | 7.6 (± 6.735) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Foveal Thickness Measured by Optical Coherence Tomography (OCT) in the Study Eye

| | |
|---|---|
| End point title | Change from Baseline in Foveal Thickness Measured by Optical Coherence Tomography (OCT) in the Study Eye |

End point description:

OCT is a laser based non-invasive diagnostic system providing high-resolution imaging sections of the fovea (part of the retina) in the study eye after pupil dilation. A negative change from baseline indicates an improvement (less foveal thickness) and a positive change from baseline indicates a worsening (more foveal thickness).

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

End point timeframe:

Baseline, Month 12

| **End point values** | dexamethasone Intravitreal Implant | ranibizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 181 | 182 | | |
| Units: Microns | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 465.1 (± 136.09) | 471.2 (± 139.51) | | |
| Change from Baseline at Month 12 (N=163, 166) | -173.9 (± 129.64) | -163.5 (± 161.34) | | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline in Total Area of Macular Leakage in the Study Eye Measured on Fluorescein Angiography (FA)**

| End point title | Change from Baseline in Total Area of Macular Leakage in the Study Eye Measured on Fluorescein Angiography (FA) |
|---|---|

End point description:

FA is a technique for examining the circulation of the retina (and detecting any leakage) using a dye-tracing method. Photographs are taken with a specialized low-power microscope with an attached camera designed to photograph the interior of the eye, including the retina and optic disc. A negative change from baseline indicates a decrease in leakage (improvement) and a positive change from baseline indicates an increase in leakage (worsening).

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

End point timeframe:

Baseline, Month 12

| **End point values** | dexamethasone Intravitreal Implant | ranibizumab | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 172 | 177 | | |
| Units: Square Millimeters (mm^2) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 19.2 (± 13.01) | 18.9 (± 12.55) | | |

| | | | | |
|---|---|---|---|---|
| Change from Baseline at Month 12 (N=125, 142) | -16.1 (± 11.64) | -12 (± 10.54) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAE) are reported and include all adverse events (AEs) and serious adverse events (SAEs) that began or worsened after study treatment.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 16.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | dexamethasone Intravitreal Implant |

Reporting group description:

Injection of 700 ug dexamethasone intravitreal implant into the study eye on Day 1, Month 5, and Month 10.

| | |
|---|---|
| Reporting group title | ranibizumab |

Reporting group description:

Injection of ranibizumab 0.5 mg into the study eye on Day 1. Patients may receive additional injections on a monthly basis, as needed, for disease progression.

| Serious adverse events | dexamethasone Intravitreal Implant | ranibizumab | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 40 / 181 (22.10%) | 41 / 182 (22.53%) | |
| number of deaths (all causes) | 3 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal Cell Carcinoma | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder Transitional Cell Carcinoma | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung Squamous Cell Carcinoma Metastatic | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Mantle Cell Lymphoma | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neoplasm Malignant | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate Cancer | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous Cell Carcinoma of the Tongue | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon Cancer | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic Carcinoma | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous Cell Carcinoma | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertensive Crisis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Ischaemia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral Vascular Disorder | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Cardiac Pacemaker Insertion | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liposuction | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest Pain | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Local Swelling | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Pyrexia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 182 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised Oedema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Endometrial Hyperplasia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute Respiratory Failure | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Respiratory Depression | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Oedema | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Intraocular Pressure Increased | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight Decreased | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Hip Fracture | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post Procedural Haemorrhage | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Fracture | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tendon Rupture | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Femoral Neck Fracture | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hand Fracture | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus Fracture | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post Procedural Haematoma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary Artery Disease | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 2 / 182 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Pectoris | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 182 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Cardiac Failure | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial Infarction | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericardial Effusion | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial Ischaemia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 182 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aortic Valve Stenosis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Ventricular Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Grand Mal Convulsion | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningorrhagia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular Accident | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic Stroke | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient Ischaemic Attack | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 2 / 182 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Sudden Hearing Loss | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Open Angle Glaucoma | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Choroiditis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lacrimation Increased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vitreous Haemorrhage | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|---|---|---|
| Colitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal Ulcer Haemorrhage | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inguinal Hernia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 182 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Jaundice | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic Foot | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal Failure Acute | | | |
| subjects affected / exposed | 4 / 181 (2.21%) | 3 / 182 (1.65%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Failure Chronic | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephropathy | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal Failure | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Rotator Cuff Syndrome | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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|---|---|---|---|
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Sepsis | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 2 / 182 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endophthalmitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound Infection | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess Limb | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal Abscess | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney Infection | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sialoadenitis | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Wall Abscess | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atypical Pneumonia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected Bites | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic Shock | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Hypoglycaemia | | | |
| subjects affected / exposed | 2 / 181 (1.10%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 181 (0.55%) | 0 / 182 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes Mellitus Inadequate Control | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 2 / 182 (1.10%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic Acidosis | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Type 2 Diabetes Mellitus | | | |
| subjects affected / exposed | 0 / 181 (0.00%) | 1 / 182 (0.55%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

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

| **Non-serious adverse events** | dexamethasone Intravitreal Implant | ranibizumab | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 160 / 181 (88.40%) | 104 / 182 (57.14%) | |
| Investigations | | | |
| Intraocular Pressure Increased | | | |
| subjects affected / exposed | 65 / 181 (35.91%) | 12 / 182 (6.59%) | |
| occurrences (all) | 117 | 22 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 8 / 181 (4.42%) | 10 / 182 (5.49%) | |
| occurrences (all) | 11 | 10 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 181 (3.31%) | 10 / 182 (5.49%) | |
| occurrences (all) | 5 | 14 | |
| Eye disorders | | | |
| Conjunctival Haemorrhage | | | |
| subjects affected / exposed | 36 / 181 (19.89%) | 24 / 182 (13.19%) | |
| occurrences (all) | 51 | 52 | |
| Cataract | | | |
| subjects affected / exposed | 28 / 181 (15.47%) | 8 / 182 (4.40%) | |
| occurrences (all) | 33 | 13 | |
| Vitreous Haemorrhage | | | |
| subjects affected / exposed | 22 / 181 (12.15%) | 7 / 182 (3.85%) | |
| occurrences (all) | 27 | 7 | |
| Visual Acuity Reduced | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 14 / 181 (7.73%) | 5 / 182 (2.75%) | |
| occurrences (all) | 16 | 6 | |
| Cataract Subcapsular | | | |
| subjects affected / exposed | 14 / 181 (7.73%) | 1 / 182 (0.55%) | |
| occurrences (all) | 20 | 2 | |
| Vitreous Floaters | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 13 / 181 (7.18%) | 2 / 182 (1.10%) | |
| occurrences (all) | 20 | 6 | |
| Ocular Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 181 (6.08%) | 2 / 182 (1.10%) | |
| occurrences (all) | 19 | 3 | |
| Eye Pain | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 10 / 181 (5.52%) | 6 / 182 (3.30%) | |
| occurrences (all) | 15 | 7 | |
| Diabetic Retinal Oedema | | | |
| subjects affected / exposed | 10 / 181 (5.52%) | 5 / 182 (2.75%) | |
| occurrences (all) | 11 | 6 | |
| Vitreous Detachment | | | |
| subjects affected / exposed | 10 / 181 (5.52%) | 5 / 182 (2.75%) | |
| occurrences (all) | 11 | 8 | |
| Punctate Keratitis | | | |
| subjects affected / exposed | 9 / 181 (4.97%) | 3 / 182 (1.65%) | |
| occurrences (all) | 9 | 3 | |
| Macular Oedema | | | |
| subjects affected / exposed | 3 / 181 (1.66%) | 10 / 182 (5.49%) | |
| occurrences (all) | 3 | 15 | |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 9 / 181 (4.97%) | 4 / 182 (2.20%) | |
| occurrences (all) | 9 | 4 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported