



## Clinical trial results:

### A Prospective Randomised Controlled Trial of Intravitreal Ozurdex and Macular Laser Therapy versus Macular Laser Therapy only in Diabetic Macular Oedema (OZLASE study)

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-003339-74  |
| Trial protocol           | GB              |
| Global end of trial date | 22 October 2013 |

#### Results information

|                                   |                                  |
|-----------------------------------|----------------------------------|
| Result version number             | v1 (current)                     |
| This version publication date     | 01 August 2019                   |
| First version publication date    | 01 August 2019                   |
| Summary attachment (see zip file) | Abstract (ABSTRACT - OZLASE.pdf) |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | HYKP1016 |
|-----------------------|----------|

##### Additional study identifiers

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

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Moorfields Eye Hospital NHS Foundation Trust                              |
| Sponsor organisation address | 162, City Road, London, United Kingdom, EC1V 2PD                          |
| Public contact               | Tania West, Moorfields Eye Hospital, 0044 2075662937, tania.west2@nhs.net |
| Scientific contact           | Tania West, Moorfields Eye Hospital, 0044 2075662937, tania.west2@nhs.net |

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:

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**Results analysis stage**

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|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 22 October 2013 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 22 October 2013 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 22 October 2013 |
| Was the trial ended prematurely?                     | No              |

Notes:

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**General information about the trial**

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Main objective of the trial:

To study the relative efficacy of repeated intravitreal Ozurdex + macular laser therapy versus macular laser therapy only in improving visual acuity and anatomical changes in eyes with diabetic macular oedema (DMO).

Protection of trial subjects:

This trial is designed as a randomised clinical trial so that a direct comparison can be made between subjects

receiving the combination therapy of ozurdex and macular laser therapy and macular laser therapy alone. While

diabetic eye disease may affect both eyes of a single subject in a similar way, this is not always the case.

In subjects where only one eye meets the inclusion criteria: the fellow eye (nonstudy eye) will be monitored during the

course of the study by the trial investigators and will receive macular laser therapy in accordance with the NHS

standard of care. In subjects where both eyes meet the inclusion criteria: the eye with the worse visual acuity will be

included in the study and become the study eye. The fellow eye (nonstudy

eye) will be treated in accordance with

macular laser therapy as part of the NHS standard of care, and will continue to be monitored by the study investigators

throughout the study and receive further treatment if required in accordance with the standard guidelines for treating

diabetic eye disease.

Study data will be anonymised to ensure compliance with the data protection act and patients will be given as much

time as they need to decide whether they wish to participate in the study. All the research team are trained in GCP

Background therapy:

The intervention arm of this study will receive 2 mandated doses of Ozurdex at baseline and 16 weeks and then repeated intravitreal Ozurdex and macular laser therapy at weeks 32 and 48 if retreatment criteria are met. The comparison group in the control arm of this study will receive macular laser therapy to the study eye at weeks 0, and at weeks 16, 32 and 48 if retreatment criteria are met.

Treatment will be performed in both study arms according to modified ETDRS guidelines which is the current standard of care in UK clinical practice.

Evidence for comparator:

Treatment will be performed in both study arms according to modified ETDRS guidelines which is the current standard of care in UK clinical practice.

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 15 September 2011 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

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|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 80 |
| Worldwide total number of subjects   | 80                 |
| EEA total number of subjects         | 80                 |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 43 |
| From 65 to 84 years                       | 35 |
| 85 years and over                         | 2  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 219 patients were enrolled from October 2011 to August 2012 from Medical Retina Clinics at Moorfields Eye Hospital and its satellites. One eye per patient was enrolled in the trial. If both eyes of the patient met the eligibility criteria, the eye with the worse BCVA at baseline was designated as the study eye.

### Pre-assignment

Screening details:

Full ophthalmic and medical history, refracted best corrected visual acuity, ophthalmic examination, LOCS II and IOP, blood pressure, HbA1C blood test, VFQ-25 and EQ-5D. Pregnancy test will be undertaken. Pupil dilation, 4-field stereo fundus photography, fluorescein angiography, and optical coherence tomography performed.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 80 |
| Number of subjects completed | 80 |

### Period 1

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

Blinding implementation details:

The visual acuity examiners and OCT technicians (i.e. assessors) masked to the subject study arm. A masked observer used to determine whether a 10 or more decrease in BCVA letter score is attributable to cataract.

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | combination arm of Ozurdex and laser photocoagulation |

Arm description:

The patients randomised to the combination arm received two mandated doses of Ozurdex at baseline and at week 16. Further re-treatment occurred at 32 or 48 weeks with a combination of Ozurdex and macular laser if retreatment criteria were met.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Ozurdex      |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Injection    |
| Routes of administration               | Other use    |

Dosage and administration details:

Patients randomized to the combination arm received 2 mandated doses of Ozurdex at screening and week 16. Further re-treatment occurred at 32 or 48 weeks with a combination of Ozurdex and modified ETDRS macular laser therapy if re-treatment criteria were met. Ozurdex administered via intravitreal injection in accordance with a trial prescription.

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

Arm description:

Patients randomized to the laser arm received modified ETDRS macular laser therapy at screening and again at 16, 32 or 48 weeks if clinically significant macula oedema was present.

|          |                   |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

|  |                   |
|--|-------------------|
| Investigational medicinal product name | Laser             |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Ophthalmic insert |
| Routes of administration               | Intraocular use   |

Dosage and administration details:

The patients randomised to the MLT arm received laser therapy according to the modified Early Treatment Diabetic Retinopathy study (ETDRS) macular laser guidelines at screening and at 16, 32 or 48 weeks if the retreatment criteria were met.

Notes:

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

Justification: Optometrists and OCT technicians were the assessors who were masked to treatment allocation

| Number of subjects in period 1 | combination arm of Ozurdex and laser photocoagulation | Laser |
|--------------------------------|---|-------|
|                                |   |       |
| Started                        | 40  | 40    |
| Completed                      | 38  | 39    |
| Not completed                  | 2   | 1     |
| Adverse event, non-fatal       | 1   | 1     |
| Lost to follow-up              | 1   | -     |

## Baseline characteristics

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | combination arm of Ozurdex and laser photocoagulation |
|-----------------------|---|

Reporting group description:

The patients randomised to the combination arm received two mandated doses of Ozurdex at baseline and at week 16. Further re-treatment occurred at 32 or 48 weeks with a combination of Ozurdex and macular laser if retreatment criteria were met.

|                       |       |
|-----------------------|-------|
| Reporting group title | Laser |
|-----------------------|-------|

Reporting group description:

Patients randomized to the laser arm received modified ETDRS macular laser therapy at screening and again at 16, 32 or 48 weeks if clinically significant macula oedema was present.

| Reporting group values  | combination arm of Ozurdex and laser photocoagulation | Laser          | Total |
|---|---|----------------|-------|
| Number of subjects  | 40  | 40             | 80    |
| Age categorical<br>Units: Subjects  |   |                |       |
| In utero  |   |                | 0     |
| Preterm newborn infants (gestational age < 37 wks)                                    |   |                | 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)  |   |                | 0     |
| From 65-84 years  |   |                | 0     |
| 85 years and over   |   |                | 0     |
| Age continuous  |   |                |       |
| Mean age in years (SD)<br>Ozurdex +laser arm - 65.6 (10.6)<br>Laser arm - 61.1 (12.8) |   |                |       |
| Units: years<br>arithmetic mean<br>standard deviation                                 | 65.6<br>± 10.6  | 61.1<br>± 12.8 | -     |
| Gender categorical<br>Units: Subjects   |   |                |       |
| Female  | 6   | 8              | 14    |
| Male  | 34  | 32             | 66    |
| Type of diabetes<br>Units: Subjects   |   |                |       |
| Type 1  | 2   | 4              | 6     |
| Type 2  | 38  | 36             | 74    |
| Visual acuity group<br>Units: Subjects  |   |                |       |
| 54-66 letters   | 22  | 21             | 43    |
| 67-78 letters   | 18  | 19             | 37    |
| Lens status<br>Units: Subjects  |   |                |       |

|              |    |    |    |
|--------------|----|----|----|
| Pseudophakic | 13 | 13 | 26 |
| Phakic       | 27 | 27 | 54 |

|  |                     |                    |   |
|--|---------------------|--------------------|---|
| Duration of diabetes mellitus<br>Units: years<br>median<br>inter-quartile range (Q1-Q3)            | 15<br>11 to 20      | 15<br>9 to 22.5    | - |
| HbA1c<br>Units: percent<br>arithmetic mean<br>standard deviation                                   | 7.9<br>± 1.2        | 8.0<br>± 1.4       | - |
| Systolic BP<br>Units: mmHg<br>arithmetic mean<br>standard deviation                                | 130.7<br>± 16.6     | 130.8<br>± 16.0    | - |
| Diastolic BP<br>Units: mmHg<br>arithmetic mean<br>standard deviation                               | 72<br>± 9.4         | 76.1<br>± 9.2      | - |
| ETDRS BCVA<br>Units: letters<br>arithmetic mean<br>standard deviation                              | 66.1<br>± 7.3       | 66.6<br>± 7.7      | - |
| Duration of CSMO<br>Units: months<br>median<br>inter-quartile range (Q1-Q3)                        | 25.5<br>7.5 to 40.5 | 41<br>23.5 to 83.5 | - |
| number of prior macular laser therapies<br>Units: number<br>median<br>inter-quartile range (Q1-Q3) | 2<br>1 to 3         | 3<br>2 to 4        | - |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | combination arm of Ozurdex and laser photocoagulation |
| Reporting group description:<br>The patients randomised to the combination arm received two mandated doses of Ozurdex at baseline and at week 16. Further re-treatment occurred at 32 or 48 weeks with a combination of Ozurdex and macular laser if retreatment criteria were met. |   |
| Reporting group title   | Laser   |
| Reporting group description:<br>Patients randomized to the laser arm received modified ETDRS macular laser therapy at screening and again at 16, 32 or 48 weeks if clinically significant macula oedema was present.  |   |

### Primary: Difference in mean best corrected ETDRS visual acuity (BCVA) letter score at 56 weeks between the two study arms

|                                  |  |
|----------------------------------|--|
| End point title                  | Difference in mean best corrected ETDRS visual acuity (BCVA) letter score at 56 weeks between the two study arms |
| End point description:           |  |
| End point type                   | Primary  |
| End point timeframe:<br>56 weeks |  |

| End point values                     | combination arm of Ozurdex and laser photocoagulation | Laser           |  |  |
|--------------------------------------|---|-----------------|--|--|
| Subject group type                   | Reporting group                                       | Reporting group |  |  |
| Number of subjects analysed          | 40  | 40              |  |  |
| Units: ETDRS letters                 |   |                 |  |  |
| arithmetic mean (standard deviation) | -0.3 (± 11.4)   | 0.4 (± 9.5)     |  |  |

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title                                  | Intention to treat population                                 |
| Statistical analysis description:<br>Descriptive statistics |   |
| Comparison groups   | combination arm of Ozurdex and laser photocoagulation v Laser |



|   |                      |
|---|----------------------|
| Number of subjects included in analysis | 80                   |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | other <sup>[1]</sup> |
| P-value                                 | < 0.05               |
| Method                                  | t-test, 2-sided      |

Notes:

[1] - The primary analyses of efficacy parameters were performed for the ITT population. A per protocol (PP) population, including only all randomised patients that had 12-month visual acuity data, was also conducted. A sensitivity analysis was performed to estimate the effect of cataract surgery done as PP and otherwise, for patients who underwent cataract surgery during the study. Missing BCVA data were imputed with the method of last observation carried forward.

### Secondary: Patients gaining $\geq 10$ ETDRS letters at 56 weeks from baseline

|                 |  |
|-----------------|--|
| End point title | Patients gaining $\geq 10$ ETDRS letters at 56 weeks from baseline |
|-----------------|--|

End point description:

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 56 weeks             |           |

| End point values                   | combination arm of Ozurdex and laser photocoagulation | Laser           |  |  |
|------------------------------------|---|-----------------|--|--|
| Subject group type                 | Reporting group                                       | Reporting group |  |  |
| Number of subjects analysed        | 38  | 39              |  |  |
| Units: number of participants/eyes | 7   | 8               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients gaining $\geq 15$ ETDRS letters at 56 weeks from baseline

|                 |  |
|-----------------|--|
| End point title | Patients gaining $\geq 15$ ETDRS letters at 56 weeks from baseline |
|-----------------|--|

End point description:

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| 56 weeks             |           |

|                                    |   |                 |  |  |
|------------------------------------|---|-----------------|--|--|
| <b>End point values</b>            | combination arm of Ozurdex and laser photocoagulation | Laser           |  |  |
| Subject group type                 | Reporting group                                       | Reporting group |  |  |
| Number of subjects analysed        | 38  | 39              |  |  |
| Units: number of participants/eyes | 6   | 2               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients losing <15 ETDRS letters at 56 weeks from baseline,

|                        |  |
|------------------------|--|
| End point title        | Patients losing <15 ETDRS letters at 56 weeks from baseline, |
| End point description: |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| 56 weeks               |  |

|                                    |   |                 |  |  |
|------------------------------------|---|-----------------|--|--|
| <b>End point values</b>            | combination arm of Ozurdex and laser photocoagulation | Laser           |  |  |
| Subject group type                 | Reporting group                                       | Reporting group |  |  |
| Number of subjects analysed        | 38  | 39              |  |  |
| Units: Number of participants/eyes | 35  | 35              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients losing ≥30 ETDRS letters at 56 weeks from baseline

|                        |   |
|------------------------|---|
| End point title        | Patients losing ≥30 ETDRS letters at 56 weeks from baseline |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| 56 weeks               |   |

|                                     |   |                 |  |  |
|-------------------------------------|---|-----------------|--|--|
| <b>End point values</b>             | combination arm of Ozurdex and laser photocoagulation | Laser           |  |  |
| Subject group type                  | Reporting group                                       | Reporting group |  |  |
| Number of subjects analysed         | 38  | 39              |  |  |
| Units: number of participants/ eyes | 1   | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in ETDRS BCVA at 24 weeks from baseline

|                        |  |
|------------------------|--|
| End point title        | Change in ETDRS BCVA at 24 weeks from baseline |
| End point description: |  |
| End point type         | Secondary                                      |
| End point timeframe:   |  |
| 56 weeks               |  |

|                                      |   |                   |  |  |
|--------------------------------------|---|-------------------|--|--|
| <b>End point values</b>              | combination arm of Ozurdex and laser photocoagulation | Laser             |  |  |
| Subject group type                   | Reporting group                                       | Reporting group   |  |  |
| Number of subjects analysed          | 40  | 40                |  |  |
| Units: ETDRS letters                 |   |                   |  |  |
| arithmetic mean (standard deviation) | 1.3 ( $\pm$ 8.8)                                      | -0.7 ( $\pm$ 6.3) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change in ETDRS BCVA at 40 weeks from baseline

|                        |  |
|------------------------|--|
| End point title        | Change in ETDRS BCVA at 40 weeks from baseline |
| End point description: |  |
| End point type         | Secondary                                      |
| End point timeframe:   |  |
| 56 weeks               |  |

| <b>End point values</b>              | combination<br>arm of Ozurdex<br>and laser<br>photocoagulation | Laser           |  |  |
|--------------------------------------|--|-----------------|--|--|
| Subject group type                   | Reporting group  | Reporting group |  |  |
| Number of subjects analysed          | 40   | 40              |  |  |
| Units: ETDRS letters                 |  |                 |  |  |
| arithmetic mean (standard deviation) | -1.1 (± 12.8)  | -0.1 (± 6.8)    |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

56 weeks

Adverse event reporting additional description:

All adverse events (AEs) were recorded in the medical records and CRF until the patient completed their wk 56 visit. Severity, causality and expectedness were defined in the protocol and the SPC. All SAEs/SARs were recorded on the SAE form and reported to the sponsor within one working day unless otherwise specified in the protocol.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

|                 |      |
|-----------------|------|
| Dictionary name | None |
|-----------------|------|

|                    |     |
|--------------------|-----|
| Dictionary version | 0.0 |
|--------------------|-----|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | combination arm of Ozurdex and laser photocoagulation |
|-----------------------|---|

Reporting group description:

The patients randomised to the combination arm received two mandated doses of Ozurdex at baseline and at week 16. Further re-treatment occurred at 32 or 48 weeks with a combination of Ozurdex and macular laser if retreatment criteria were met.

|                       |       |
|-----------------------|-------|
| Reporting group title | Laser |
|-----------------------|-------|

Reporting group description:

Patients randomized to the laser arm received modified ETDRS macular laser therapy at screening and again at 16, 32 or 48 weeks if clinically significant macula oedema was present.

| Serious adverse events                            | combination arm of Ozurdex and laser photocoagulation | Laser          |  |
|---|---|----------------|--|
| Total subjects affected by serious adverse events |   |                |  |
| subjects affected / exposed                       | 15 / 40 (37.50%)                                      | 3 / 40 (7.50%) |  |
| number of deaths (all causes)                     | 0   | 0              |  |
| number of deaths resulting from adverse events    | 0   | 0              |  |
| Cardiac disorders                                 |   |                |  |
| Arrhythmia  |   |                |  |
| subjects affected / exposed                       | 0 / 40 (0.00%)  | 2 / 40 (5.00%) |  |
| occurrences causally related to treatment / all   | 0 / 0   | 0 / 2          |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0          |  |
| Cardiac problem (unknown) with memory loss        |   |                |  |
| subjects affected / exposed                       | 1 / 40 (2.50%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all   | 0 / 1   | 0 / 0          |  |
| deaths causally related to treatment / all        | 0 / 0   | 0 / 0          |  |
| Nervous system disorders                          |   |                |  |
| Cerebrovascular accident                          |   |                |  |

|   |  |                |  |
|---|--|----------------|--|
| subjects affected / exposed                     | 0 / 40 (0.00%)   | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Social circumstances                            |  |                |  |
| Admitted to care home for rehabilitation        |  |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)   | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Eye disorders                                   |  |                |  |
| Cataract surgery - study eye                    |  |                |  |
| subjects affected / exposed                     | 9 / 40 (22.50%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 5 / 9  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| cataract surgery - fellow eye                   |  |                |  |
| subjects affected / exposed                     | 3 / 40 (7.50%)   | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Endonasal dacryocystorhinostomy - fellow eye    |  |                |  |
| subjects affected / exposed                     | 1 / 40 (2.50%)   | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Raised intra-ocular pressure                    | Additional description: IOP >45 mmHg was defined as an SAE in the protocol |                |  |
| subjects affected / exposed                     | 1 / 40 (2.50%)   | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Ptosis repair                                   |  |                |  |
| subjects affected / exposed                     | 1 / 40 (2.50%)   | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0          |  |
| Vitreous haemorrhage                            |  |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)   | 1 / 40 (2.50%) |  |
| 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        |   |                |  |
| Vaginal candidiasis                             |   |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)                          | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0                                   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Gastrointestinal disorders                      |   |                |  |
| Gastric bypass                                  |   |                |  |
| subjects affected / exposed                     | 1 / 40 (2.50%)                          | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Hepatobiliary disorders                         |   |                |  |
| Cholecystitis                                   | Additional description: hospitalisation |                |  |
| subjects affected / exposed                     | 1 / 40 (2.50%)                          | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Renal and urinary disorders                     |   |                |  |
| Urinary tract infection                         |   |                |  |
| subjects affected / exposed                     | 1 / 40 (2.50%)                          | 2 / 40 (5.00%) |  |
| occurrences causally related to treatment / all | 0 / 1                                   | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Renal failure                                   |   |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)                          | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0                                   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Urinary retention                               | Additional description: Hospitalisation |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)                          | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0                                   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Flank pain                                      |   |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)                          | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0                                   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0                                   | 0 / 0          |  |
| Endocrine disorders                             |   |                |  |
| Diabetic ketoacidosis                           | Additional description: Hospitalisation |                |  |

|   |   |                |  |
|---|---|----------------|--|
| subjects affected / exposed                     | 0 / 40 (0.00%)  | 1 / 40 (2.50%) |  |
| 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 |   |                |  |
| Osteomyelitis                                   |   |                |  |
| subjects affected / exposed                     | 1 / 40 (2.50%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Back surgery                                    |   |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)  | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Amputation                                      |   |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)  | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Fracture neck of femur                          |   |                |  |
|   | Additional description: Hospitalisation for surgery             |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)  | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Product issues                                  |   |                |  |
| Device failure                                  |   |                |  |
|   | Additional description: Fragmented implant/incomplete insertion |                |  |
| subjects affected / exposed                     | 3 / 40 (7.50%)  | 0 / 40 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3   | 0 / 0          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |
| Infections and infestations                     |   |                |  |
| Salmonella infection                            |   |                |  |
| subjects affected / exposed                     | 0 / 40 (0.00%)  | 1 / 40 (2.50%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0          |  |

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



| Non-serious adverse events   | combination arm of Ozurdex and laser photocoagulation                                 | Laser  |  |
|--|---|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed   | 35 / 40 (87.50%)  | 24 / 40 (60.00%)                               |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>Melanoma<br>subjects affected / exposed<br>occurrences (all)  | 0 / 40 (0.00%)<br>0   | 1 / 40 (2.50%)<br>1                            |  |
| General disorders and administration site conditions<br>Intermittent pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 40 (0.00%)<br>0   | 1 / 40 (2.50%)<br>1                            |  |
| Respiratory, thoracic and mediastinal disorders<br>Respiratory infection<br>subjects affected / exposed<br>occurrences (all)<br><br>Breathing difficulty and cough<br>subjects affected / exposed<br>occurrences (all) | 2 / 40 (5.00%)<br>2<br><br>2 / 40 (5.00%)<br>2  | 2 / 40 (5.00%)<br>2<br><br>0 / 40 (0.00%)<br>0 |  |
| Product issues<br>Device fault<br>subjects affected / exposed<br>occurrences (all)   | Additional description: Drug packaging contained no drug                              |  |  |
|  | 1 / 40 (2.50%)<br>1   | 0 / 40 (0.00%)<br>0                            |  |
| Injury, poisoning and procedural complications<br>Fluorescein angiography complications<br>subjects affected / exposed<br>occurrences (all)  | Additional description: adverse reaction, extravasation of dye, difficult cannulation |  |  |
|  | 2 / 40 (5.00%)<br>2   | 2 / 40 (5.00%)<br>2                            |  |
| Cardiac disorders<br>Raised blood pressure<br>subjects affected / exposed<br>occurrences (all)<br><br>Cardiac failure<br>subjects affected / exposed<br>occurrences (all)  | 1 / 40 (2.50%)<br>1<br><br>1 / 40 (2.50%)<br>1  | 0 / 40 (0.00%)<br>0<br><br>0 / 40 (0.00%)<br>0 |  |
| Nervous system disorders   |   |  |  |

|   |   |                      |  |
|---|---|----------------------|--|
| Confusion and drowsiness<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 40 (2.50%)<br>1                                 | 1 / 40 (2.50%)<br>1  |  |
| Left sided weakness and dysphasia<br>subjects affected / exposed<br>occurrences (all)                 | Additional description: Residual sequelae of stroke |                      |  |
| Amnesia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 40 (0.00%)<br>0                                 | 1 / 40 (2.50%)<br>1  |  |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)           | 1 / 40 (2.50%)<br>1                                 | 0 / 40 (0.00%)<br>0  |  |
| Eye disorders<br>Cataract progression - study eye<br>subjects affected / exposed<br>occurrences (all) | 21 / 40 (52.50%)<br>21                              | 4 / 40 (10.00%)<br>4 |  |
| Cataract progression non study eye<br>subjects affected / exposed<br>occurrences (all)                | 5 / 40 (12.50%)<br>5                                | 0 / 40 (0.00%)<br>0  |  |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 40 (2.50%)<br>1                                 | 1 / 40 (2.50%)<br>1  |  |
| Corneal adverse events<br>subjects affected / exposed<br>occurrences (all)                            | Additional description: Foreign body/abrasion/scar  |                      |  |
| Progression of macular oedema - study eye<br>subjects affected / exposed<br>occurrences (all)         | 2 / 40 (5.00%)<br>3                                 | 0 / 40 (0.00%)<br>0  |  |
| Progression of macular oedema - fellow eye<br>subjects affected / exposed<br>occurrences (all)        | 1 / 40 (2.50%)<br>1                                 | 1 / 40 (2.50%)<br>1  |  |
| Floaters -study eye<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 40 (5.00%)<br>2                                 | 2 / 40 (5.00%)<br>2  |  |
| Raised intraocular pressure   | 5 / 40 (12.50%)<br>6                                | 0 / 40 (0.00%)<br>0  |  |

|  |                  |                 |
|--|------------------|-----------------|
| subjects affected / exposed                                    | 8 / 40 (20.00%)  | 1 / 40 (2.50%)  |
| occurrences (all)  | 9                | 1               |
| Eye pain   |                  |                 |
| subjects affected / exposed                                    | 5 / 40 (12.50%)  | 1 / 40 (2.50%)  |
| occurrences (all)  | 5                | 1               |
| Posterior capsular opacification - study eye                   |                  |                 |
| subjects affected / exposed                                    | 0 / 40 (0.00%)   | 2 / 40 (5.00%)  |
| occurrences (all)  | 0                | 0               |
| Progression to proliferative diabetic retinopathy- study eye   |                  |                 |
| subjects affected / exposed                                    | 1 / 40 (2.50%)   | 4 / 40 (10.00%) |
| occurrences (all)  | 1                | 5               |
| Progression to proliferative diabetic retinopathy - fellow eye |                  |                 |
| subjects affected / exposed                                    | 4 / 40 (10.00%)  | 4 / 40 (10.00%) |
| occurrences (all)  | 5                | 5               |
| Ptosis   |                  |                 |
| subjects affected / exposed                                    | 3 / 40 (7.50%)   | 0 / 40 (0.00%)  |
| occurrences (all)  | 3                | 0               |
| Subconjunctival hemorrhage                                     |                  |                 |
| subjects affected / exposed                                    | 15 / 40 (37.50%) | 0 / 40 (0.00%)  |
| occurrences (all)  | 20               | 0               |
| Post injection uveitis   |                  |                 |
| subjects affected / exposed                                    | 1 / 40 (2.50%)   | 0 / 40 (0.00%)  |
| occurrences (all)  | 1                | 0               |
| Blurred vision - study eye                                     |                  |                 |
| subjects affected / exposed                                    | 7 / 40 (17.50%)  | 0 / 40 (0.00%)  |
| occurrences (all)  | 7                | 0               |
| visual field defect  |                  |                 |
| subjects affected / exposed                                    | 0 / 40 (0.00%)   | 1 / 40 (2.50%)  |
| occurrences (all)  | 0                | 1               |
| vitreous hemorrhage - study eye                                |                  |                 |
| subjects affected / exposed                                    | 2 / 40 (5.00%)   | 2 / 40 (5.00%)  |
| occurrences (all)  | 2                | 4               |
| Vitreous haemorrhage- fellow eye                               |                  |                 |

|  |                     |                     |  |
|--|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 40 (0.00%)<br>0 | 2 / 40 (5.00%)<br>2 |  |
| Gastrointestinal disorders<br>Nausea and vomiting<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 40 (2.50%)<br>1 | 2 / 40 (5.00%)<br>3 |  |
| Skin and subcutaneous tissue disorders<br>Boils<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 40 (2.50%)<br>1 | 0 / 40 (0.00%)<br>0 |  |
| Renal and urinary disorders<br>Nephrotic syndrome with kidney<br>infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 40 (0.00%)<br>0 | 1 / 40 (2.50%)<br>1 |  |
| Endocrine disorders<br>Hypoglycemic episode<br>subjects affected / exposed<br>occurrences (all)                                | 1 / 40 (2.50%)<br>1 | 0 / 40 (0.00%)<br>0 |  |
| Fluctuating diabetic control<br>subjects affected / exposed<br>occurrences (all)   | 0 / 40 (0.00%)<br>0 | 1 / 40 (2.50%)<br>1 |  |
| Musculoskeletal and connective tissue<br>disorders<br>Infection<br>subjects affected / exposed<br>occurrences (all)            | 1 / 40 (2.50%)<br>2 | 1 / 40 (2.50%)<br>1 |  |
| Infections and infestations<br>Flu with gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 40 (2.50%)<br>1 | 1 / 40 (2.50%)<br>1 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 14 October 2013 | <p>Amendment to the protocol, consent form and patient information sheet.</p> <p>The substantial amendment of the protocol, PIS and consent was a retrospective amendment to cover what was actually been undertaken for the study. This included the following:</p> <ul style="list-style-type: none"><li>• Inclusion of cataract surgery within the study and clarification of referral for surgery</li><li>• Definition of cataract</li><li>• Amendment of the safety definitions and management of the study</li><li>• Amendment of the SAP for the study</li></ul> |

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.

The study did not have an Ozurdex monotherapy arm to evaluate the effect of withholding MLT completely.  
Under-reporting of AEs/SAEs was detected by QA and led to recognition of cataract as a SUSAR due to higher than expected frequency of occurrence.

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26472406>