



Clinical trial results:

Preoperative intravitreal ranibizumab for persistent diabetic vitreous haemorrhage: A randomized, double-masked, controlled study

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2009-015559-25 |
| Trial protocol | GB |
| Global end of trial date | 20 October 2015 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 06 March 2019 |
| First version publication date | 06 March 2019 |
| Summary attachment (see zip file) | FINAL STUDY REPORT (PARADISE Final Report 31.08.2017.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | KCH1724 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01030770 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | King's College Hospital NHS Foundation Trust |
| Sponsor organisation address | Denmark Hill, London, United Kingdom, SE5 9RS |
| Public contact | Mr Tim Jackson, King's College Hospital NHS Foundation Trust, 020 020 3299 1297, tim1.jackson@kcl.ac.uk |
| Scientific contact | Mr Tim Jackson, King's College Hospital NHS Foundation Trust, 020 020 3299 1297, tim1.jackson@kcl.ac.uk |

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 | 20 October 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 October 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 October 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine if a single preoperative eye injection of ranibizumab (Lucentis) can promote clearance of persistent haemorrhage in the inner cavity of the eye, and thereby avoid pars plana vitrectomy (eye surgery to remove the blood inside the eye).

Protection of trial subjects:

Subjects will be provided with a Patient Information Sheet (PIS) and time to consider the contents of this document. They will have the opportunity to discuss alternative treatment options and possible enrolment in the study with the Investigator, prior to providing written informed consent

Background therapy:

None

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 30 November 2010 |
| 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 Kingdom: 24 |
| Worldwide total number of subjects | 24 |
| EEA total number of subjects | 24 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 24 |
| From 65 to 84 years | 0 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

Participants recruited from two centers in London UK between 2010 and 2015

Pre-assignment

Screening details:

- * manifest refraction and best corrected ETDRS visual acuity
- * medical and ophthalmic history
- * dynamic B mode ultrasound examination
- * slit-lamp examination of the anterior segment
- * biomicroscopy of the vitreous and fundus, and LOCSII grading of any lens opacity.
- * Intraocular pressure measurement.
- * digital fundus photography

Period 1

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

Blinding implementation details:

Patients will be randomly allocated to either treatment arm (Arm A) or placebo arm (Arm B) and will be masked to which group they have been allocated to. Both groups will undergo the same procedure preparation and follow up, with only the injection varying between the groups

Arms

| | |
|------------------------------|--------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group A - Lucentis |

Arm description:

Single 500 microgram (0.05mls) intravitreal injection of ranibizumab

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Lucentis |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

Single 500 microgram (0.05mls) intravitreal injection of ranibizumab

| | |
|------------------|------------------|
| Arm title | Group B -Placebo |
|------------------|------------------|

Arm description:

Single 0.05mls subconjunctival injection of 0.9% sodium chloride (placebo)

| | |
|--|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | 0.9% Sodium Chloride |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subconjunctival use |

Dosage and administration details:

Single 0.05mls subconjunctival injection of 0.9% sodium chloride (placebo)

| Number of subjects in period 1 | Group A - Lucentis | Group B -Placebo |
|---------------------------------------|--------------------|------------------|
| Started | 12 | 12 |
| Completed | 12 | 10 |
| Not completed | 0 | 2 |
| Adverse event, serious fatal | - | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Trial |
|-----------------------|---------------|

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|---|---------------|-------|--|
| Number of subjects | 24 | 24 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 13 | 13 | |
| From 65-84 years | 9 | 9 | |
| 85 years and over | 2 | 2 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 13 | 13 | |
| Male | 11 | 11 | |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Group A - Lucentis |
| Reporting group description: Single 500 microgram (0.05mls) intravitreal injection of ranibizumab | |
| Reporting group title | Group B -Placebo |
| Reporting group description: Single 0.05mls subconjunctival injection of 0.9% sodium chloride (placebo) | |

Primary: Primary Efficacy Parameters

| | |
|---|--|
| End point title | Primary Efficacy Parameters ^[1] |
| End point description: Number of patients requiring pars plana vitrectomy at week 7 post injection | |
| End point type | Primary |
| End point timeframe: week 7 post injection | |

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: Please see attached report detailing results

| End point values | Group A - Lucentis | Group B - Placebo | | |
|-----------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: whole | 12 | 10 | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | RESULTS/PARADISE Final Report 31.08.2017.pdf |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Efficacy Parameters

| | |
|---|-------------------------------|
| End point title | Secondary Efficacy Parameters |
| End point description: Number of patients requiring pars plana vitrectomy at study end 2. Mean duration from baseline to primary pars plana vitrectomy 3. Number of intraocular procedures required 4. Mean ETDRS visual acuity 5. Mean grade of vitreous haemorrhage (Grade 0-4)* assessed using masked independent reading of fundus photographs, at 6 weeks after the Lucentis® or placebo injection 6. Surgical complications 7. Grading of lens clarity using LOCS II (Lens Opacities Classification System version II)** * the grading system | |
| End point type | Secondary |

End point timeframe:

Dosing to month 12

| End point values | Group A - Lucentis | Group B - Placebo | | |
|-----------------------------|-----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 10 | | |
| Units: whole | 12 | 10 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of the trial - ie 12 months post injection

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | LUCENTIS |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | LUCENTIS | PLACEBO | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 12 (25.00%) | |
| number of deaths (all causes) | 0 | 2 | |
| number of deaths resulting from adverse events | 0 | 2 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| T-wave inversion | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary Occlusion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Complete heart block | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Coronary Artery Disease | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| 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 | | | |
| Exacerbation of Asthma | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Infected Skin Ulcer | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteoarthritis & knee pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | LUCENTIS | PLACEBO | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | 12 / 12 (100.00%) | |
| Injury, poisoning and procedural complications | | | |
| Pain from a fall | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Immune system disorders | | | |
| Penicillin allergy | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Choroidal detachment | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 7 / 12 (58.33%) | |
| occurrences (all) | 6 | 7 | |
| Cataract | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 3 / 12 (25.00%) | |
| occurrences (all) | 4 | 3 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Corneal oedema | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Diabetic macular oedema | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Diabetic maculopathy | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 12 (16.67%) | |
| occurrences (all) | 0 | 2 | |
| Disc neovascularisation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Epiretinal membrane | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 12 (8.33%) | |
| occurrences (all) | 2 | 1 | |
| Macular oedema | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 12 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Maculopathy | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Retinal tear | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 12 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rubeosis iridis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 12 (8.33%) | |
| occurrences (all) | 0 | 1 | |
| Visual field defect | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 12 (8.33%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|--|--|--|
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Respiratory, thoracic and mediastinal disorders Flu subjects affected / exposed occurrences (all) Upper Respiratory Tract Infection subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 2 / 12 (16.67%) 2 | 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 | |
| Psychiatric disorders Cognitive Changes subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 12 (8.33%) 1 | |
| Infections and infestations Chest infection subjects affected / exposed occurrences (all) Cold subjects affected / exposed occurrences (all) Infected Toe subjects affected / exposed occurrences (all) Tooth abscess subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 | 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 17 August 2010 | Administrative and REC detail changes. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported