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