Clinical trial results:
A randomised controlled trial of epimacular brachytherapy versus ranibizumab monotherapy for the treatment of subfoveal choroidal neovascularisation associated with wet age-related macular degeneration in patients who have commenced anti-VEGF therapy

Summary

EudraCT number	2009-012509-20
Trial protocol	GB
Global end of trial date	10 March 2015

Results information

Result version number	v1 (current)
This version publication date	08 March 2019
First version publication date	08 March 2019
Summary attachment (see zip file)	FINAL STUDY REPORT (MERLOT Final Study Report.pdf)

Trial information

Trial identification

Sponsor protocol code	MERLOT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01006538
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, 0044 02032991297,
Scientific contact	Mr Tim Jackson, King's College Hospital NHS Foundation Trust, 0044 02032991297,

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	10 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 March 2015
Global end of trial reached?	Yes
Global end of trial date	10 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if a new surgical device (epimacular brachytherapy (VIDION)) can reduce patients' requirement for ongoing ranibizumab eye injections (average number of injections per patient, per year) and maintain visual function (measured using an ETDRS eyechart).

Protection of trial subjects:

Safety parameters to be evaluated include incidence and severity of adverse events and ocular adverse events identified by eye examination. This will include the incidence of cataract changes and the incidence of radiation induced toxicity

Background therapy:

Subjects must have received anti-VEGF induction treatment, defined as the first three months of anti-VEGF therapy. Following this induction period, subjects must have received at least 4 additional injections of Lucentis® in no more than 12 months preceding enrolment, or 2 additional injections of Lucentis® in no more than 6 months preceding enrolment, given on an as needed basis.

Evidence for comparator: -

Actual start date of recruitment	10 November 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 363
Worldwide total number of subjects	363
EEA total number of subjects	363

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)	0
From 65 to 84 years	289
85 years and over	74

Subject disposition

Recruitment

Recruitment details:

The study enrolled 363 participants with chronic, active neovascular AMD who were receiving ranibizumab therapy at the time of
screening. Enrollment ran from November 10, 2009, through January 30, 2012.

Pre-assignment

Screening details:

Inclusion criteria completion of a loading phase of 3 anti-VEGF induction injections, followed by ongoing monthly
PRN therapy, with minimum of 4 ranibizumab treatments in the previous 12 months or 2 ranibizumab treatments in the previous 6
months.

Period 1

Period 1 title	Whole Group (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Masked assessment of lens opacity undertaken at Month 6, 9, 18, and 21 in both subjects & controls, if the study eye is phakic. If the study eye is pseudophakic then masked cataract assessment is not required in either eye.Masked cataract assessment should be undertaken by a Cataract Assessor who is masked to treatment allocation. Cataract Assessor must be an Ophthalmologist who has undertaken at least 400 phacoemulsification cataract operations

Arms

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

Arm description:

A single surgical procedure with epimacular brachytherapy using the VIDION® System, with Lucentis® (0.5 mg) administered on a monthly basis as required

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

Dosage and administration details:

Lucentis® (0.5 mg) administered on a monthly basis as required

Arm title	Group B - Lucentis only

Arm description:

Lucentis® (0.5 mg) administered on a monthly basis as required.

Arm type	Active comparator
Investigational medicinal product name	Lucentis
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

Lucentis® (0.5 mg) administered on a monthly basis as required.

Number of subjects in period 1	Group A - Brachytherapy + Lucentis	Group B - Lucentis only
Started	244	119
Completed	233	115
Not completed	11	4
Adverse event, serious fatal	2	-
Physician decision	4	3
Consent withdrawn by subject	5	-
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Whole Group

Reporting group description: -

Reporting group values	Whole Group	Total	
Number of subjects	363	363	
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	
Aged 56 to 96yrs	363	363	
Gender categorical Units: Subjects			
Female	217	217	
Male	146	146	

End points

End points reporting groups

Reporting group title	Group A - Brachytherapy + Lucentis

Reporting group description:

A single surgical procedure with epimacular brachytherapy using the VIDION® System, with Lucentis® (0.5 mg) administered on a monthly basis as required

Reporting group title	Group B - Lucentis only

Reporting group description:

Lucentis® (0.5 mg) administered on a monthly basis as required.

Primary: Primary Outcome

End point title	Primary Outcome[1]

End point description:

TThe coprimary outcomes, at 12 months, were the number of PRN ranibizumab injections and Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (VA).

End point type	Primary

End point timeframe:

Randomisation to 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: See attached documents for full results

End point values	Group A - Brachytherapy + Lucentis	Group B - Lucentis only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	119		
Units: whole	244	119		

Attachments (see zip file)	Results/MERLOT Final Study Report.pdf Adverse Event Listing/ADVERSE EVENT LISTINGS.pdf

Statistical analyses

No statistical analyses for this end point

Primary: Secondary Outcomes

End point title	Secondary Outcomes[2]

End point description:

Secondary outcomes included the proportion of participants losing fewer than 15 ETDRS letters, angiographic total lesion size, choroidal neovascularization (CNV) size, and optical coherence tomography (OCT) foveal thickness. A
predefined subgroup analysis tested the influence of baseline ocular characteristics on the response to EMB.

End point type	Primary

End point timeframe:

Randomisation to 12 months.

Notes:

[2] - 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: See Attached documents for full results.

End point values	Group A - Brachytherapy + Lucentis	Group B - Lucentis only		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	119		
Units: whole	244	119		

Attachments (see zip file)	Secondary Outcomes Table/Secondary outcomes table.pdf Subgroup Analysis n=Injections/Figure 7. Subgroup Analysis of Subfroup Analysis Visual Acuity/Figure 8. Subgroup Analysis of Retinal Vascular Abnormalities/Table 7. Retinal Vascular

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were reported until 12 months post randomisation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Epimacular brachytherapy + ranibizumab
Reporting group description: -	
Reporting group title	Ranibizumab Monotherapy
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Please see attached document for list of non-serious adverse events which occurred during this trial.

Serious adverse events	Epimacular brachytherapy + ranibizumab	Ranibizumab Monotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	74 / 244 (30.33%)	57 / 119 (47.90%)	
number of deaths (all causes)	14	8	
number of deaths resulting from adverse events	14	8	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Rectosigmoid carcinoma with lung and liver metastases			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endometrial carcinoma Grade 1 Stage 2.			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Cancer			
subjects affected / exposed	3 / 244 (1.23%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cancer spine			

subjects affected / exposed	1 / 244 (0.41%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Bladder Cancer			
subjects affected / exposed	1 / 244 (0.41%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast Cancer			
subjects affected / exposed	2 / 244 (0.82%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	2 / 244 (0.82%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cancer			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Cancer			
subjects affected / exposed	1 / 244 (0.41%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Malignant lump in neck			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Caecal cancer			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Cancer			

subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma Tongue			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Cancer			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Cancer			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non hodgkins B Cell lymphoma			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Sub arachnoid haemorrhage			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
vaginal hysterectomy & left salpingo oophorectomy			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fistula insertion for dialysis	Additional description: Patient had planned admission to fit fistula in left arm due to renal failure		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate HOLEP	Additional description: HOLEP – Prostate procedure caused bleeding resulting in laparotomy and death		
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Trans Urethral Retrograde Prostatectomy			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (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			
nausea, neck pain, loss of appetite			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall	Additional description: Patient had been lying on floor for up to 15 hours before she was found. Patient does not recall what happened. Pain in back and reduced mobility		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall, Confusion, UTI & Low Potassium			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Social care overnight hospital stay	Additional description: Patient stayed overnight in e Hospital following Brachytherapy surgery for social care		
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion and fall	Additional description: Confusion & fall at home - social hospital admission		

subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Stress incontinence and Vaginal prolapse			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Shortness of Breath			
subjects affected / exposed	2 / 244 (0.82%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Emphysema			
subjects affected / exposed	3 / 244 (1.23%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic chest pain			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COPD			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough & lethargy			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Acute Depression			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety Panic attack			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Attempted suicide	Additional description: Attempted suicide due to worsening visual impairment,		
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
headaches & vomiting,	Additional description: Patient suffering from headaches & vomiting, continuing stomach pain; admission to hospital for observation		
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Damage to artery requiring surgical repair during angiogram			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm repair			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Antero-lateral Myocardial infarction, subsequent pulmonary oedema with CPAP requirement			

subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulomonary embolism			
subjects affected / exposed	2 / 244 (0.82%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	4 / 244 (1.64%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Collapse after pre-syncopal event			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial fibrillation			
subjects affected / exposed	2 / 244 (0.82%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest	Additional description: Post fracture neck of femur		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Heart failure			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical Valve replacement			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospital admission for coronary artery stenting			

subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (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	3 / 244 (1.23%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Heart Palpitations			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
left bundle branch block on ECG, dilated left ventricle and globally severely impaired left ventricu			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right hemispheric TIA due to AF			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shortness of breath			
subjects affected / exposed	2 / 244 (0.82%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden onset tachycardia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid regurgitation			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left Ventricular Failure			

subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (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			
Lost consciousness after fall			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 244 (0.41%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury after fall			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shingles & relapse of Myasthenia Gravis	Additional description: Episode of shingles followed by relapse of Myasthenia Gravis. Hospilization for intravenous immunoglobulin therapy		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Vascular Accident/Stroke			
subjects affected / exposed	3 / 244 (1.23%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 1	
Rapid onset of Dementia			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suprachoroidal haemorrhage			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Grand Mal seizure			

subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headaches (NOS) Hospitalisation for tests		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blackout and fall			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Lacunar infarct with ataxic hemiparesis			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
mall lacunar infarct adjacent to frontal horn of right lateral ventricle			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizzy & unsteady on feet, marked left sided nystagmus			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Admitted to hospital with anaemia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Anaemia, admitted for blood transfusion			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis	Additional description: Admitted to hospital for right leg cellulitis and urine infection and bilateral pedal oedema		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Loss of vision, vitreous haemorrhass			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left pharcovitrectamy IOL and silicone oil procedure (non-study eye)			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	2 / 244 (0.82%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	2 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	3 / 244 (1.23%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sub-retinal haemorrhage			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-surgical severe uveitis			

subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Massive Subretinal haemorrhage			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic PED			
subjects affected / exposed	11 / 244 (4.51%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poll Central Vein Occulsion (retina) or macroaneurysm			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
visual hallucinations following surgery in both eyes			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sub retinal and sub RPE haemorrhage (study eye)			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Acute cholecystitis	Additional description: Cholecystectomy performed		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 244 (1.23%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cytomegalovirus colitis.	Additional description: Cytomegalovirus colitis leading to multi organ dysfunction.		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
strangulated umbilical hernia			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia with impending strangulation			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic bowel			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Internal Bleeding			
subjects affected / exposed	3 / 244 (1.23%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
viral diarrhoea			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
obstructive jaundice			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight loss, Diarrhoea, bowel resection			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (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			

Fall, injured right shin,	Additional description: all, injured right shin, needed skin graft to wound		
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound opening over renal dialysis fistula	Additional description: Patient admitted to hospital due to wound opening over renal dialysis fistula site		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
urinary frequency & fluid retention			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte Imbalance (patient on nocturnal dialysis)			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Acute pancreatitis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lump in neck discovered, biopsy done. R. Hemi thyroidectomy planned			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (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			
Fracture of femur			

subjects affected / exposed	1 / 244 (0.41%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Revision of previous knee replacement			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle pain, redness and swelling	Additional description: Ankle pain, redness and swelling, biopsy of ankle		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
right bimalleolar fracture			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Split Knee Cap			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured ankle			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Total Hip Replacement			
subjects affected / exposed	1 / 244 (0.41%)	4 / 119 (3.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured metatarsal after fall			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
right knee resurfacing			

subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture R Humerus following fall			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemi Arthroplasty after fall and fracture			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dislocated 4th toe on right foot after fall			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dislocated shoulder after fall			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Total knee replacement			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
1st revision total knee replacement			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
2nd revision total knee replacement			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fractured femur leading to pneumonia			

subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 244 (0.82%)	2 / 119 (1.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericarditis & Pneumonia			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder Infection			
subjects affected / exposed	1 / 244 (0.41%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess in incision scar following knee replacement surgery			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected prostate biopsy			
subjects affected / exposed	1 / 244 (0.41%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Liver abscess			
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected wound laceration left shin			

subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septicaemia			
subjects affected / exposed	3 / 244 (1.23%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Bowel and urine infection	Additional description: Routine IVIG treatment for Myasthenia Gravis -prolonged hospitalisation due to query bowel and urine infection		
subjects affected / exposed	0 / 244 (0.00%)	1 / 119 (0.84%)	
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: 0 %

Non-serious adverse events	Epimacular brachytherapy + ranibizumab	Ranibizumab Monotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 244 (0.00%)	0 / 119 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2009	Full title of the trial amended, administrative changes to addresses Changes to eligibility criteria - inclusion criterion 1 amended (Added Retinal Angiomatous Proliferation (RAP) lesions not directly involving the fovea must be associated with contiguous foveal leakage demonstrated on fundus examination, OCT, or fluorescein angiography). Exclusion criterion 2 - 24 ETDRS letters added Additional information about the EC opinion
09 June 2010	Change of Statistician. Changes to eligibility of participants and retreatment criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27086023