Clinical trial results:
A randomised controlled trial of standard and low dose Avastin® for Neovascular Macular Degeneration in the East Midlands

Summary

EudraCT number	2009-014280-38
Trial protocol	GB
Global end of trial date	31 March 2017

Results information

Result version number	v1 (current)
This version publication date	04 October 2019
First version publication date	04 October 2019

Trial information

Trial identification

Sponsor protocol code	09OY006

Additional study identifiers

ISRCTN number	ISRCTN95654194
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nottingham University Hospitals
Sponsor organisation address	Derby Road, Nottingham, United Kingdom, NG7 2UH
Public contact	R&I, Nottingham University Hospitals, 0044 0115 924 9924x6064, jennifer.boston@nuh.nhs.uk
Scientific contact	R&I, Nottingham University Hospitals, 0044 0115 924 9924x60645, jennifer.boston@nuh.nhs.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	18 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2017
Global end of trial reached?	Yes
Global end of trial date	31 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the relative effectiveness of standard versus low dose Avastin® (bevacizumab) for intravitreal injection on visual outcome in patients with nAMD.

Protection of trial subjects:

None

Background therapy:

None

Evidence for comparator:

N/A

Actual start date of recruitment	01 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 812
Worldwide total number of subjects	812
EEA total number of subjects	812

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)	20
From 65 to 84 years	576
85 years and over	216

Subject disposition

Recruitment

Recruitment details:

Participants recruited from 5 UK (East Midlands) centres between November 2010 and March 2017.

Pre-assignment

Screening details:

Any patient eligible for anti-VEGF treatment in the NHS. The treating clinician will decide if the patient is likely to benefit.

Pre-assignment period milestones

Number of subjects started	812
Number of subjects completed	812

Period 1

Period 1 title	Visit A (baseline)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

All but the pharmacist (who has no other role in the trial) are double blind to dose, but review schedule (revealed after induction) is not blinded (not possible to).

Arms

Are arms mutually exclusive?	Yes
Arm title	L1 arm

Arm description:

Low dose, monthly review

Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

0.625mg monthly (if required after first three injections)

Arm title	S1 arm

Arm description:

Standard dose, monthly review

Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

1.25mg monthly (if required after first three injections)

Arm title	L2 arm

Arm description:	
Low dose, bi-monthly review	
Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use
Dosage and administration details:	
0.625mg monthly for first three injections, then bi-monthly if required	
Arm title	S2 arm
Arm description:	
Standard dose, bi-monthly review	
Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use
Dosage and administration details:	
1.25mg monthly for first three injections, then bi-monthly if required	

Number of subjects in period 1	L1 arm	S1 arm	L2 arm
Started	204	203	203
Completed	204	203	203

Number of subjects in period 1	S2 arm
Started	202
Completed	202

Period 2	
Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor
Blinding implementation details:	
Dose was double blind to all but pharmacist, but review interview ("schedule") was not - not possible to blind.	

Arms	
Are arms mutually exclusive?	Yes

Arm title	L1 - low dose monthly
Arm description: Low dose, monthly review	
Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use
Dosage and administration details: 0.625mg monthly (if required after first three injections)	
Arm title	S1 - standard dose monthly
Arm description: Standard dose, monthly review	
Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use
Dosage and administration details: 1.25mg monthly (if required after first three injections)	
Arm title	L2 - low dose bi-monthly
Arm description: Low dose, bi-monthly review	
Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use
Dosage and administration details: 0.625mg monthly for first three injections, then bi-monthly if required	
Arm title	S2 - standard dose bi-monthly
Arm description: Standard dose, bi-monthly review	
Arm type	Active comparator
Investigational medicinal product name	bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Suspension for injection in pre-filled syringe
Routes of administration	Intravitreal use
Dosage and administration details: 1.25mg monthly for first three injections, then bi-monthly if required	

Number of subjects in period 2	L1 - low dose monthly	S1 - standard dose monthly	L2 - low dose bi-monthly
Started	204	203	203
Completed	204	203	203

Number of subjects in period 2	S2 - standard dose bi-monthly
Started	202
Completed	202

Baseline characteristics

Reporting groups	
Reporting group title	L1 arm
Reporting group description:	
Low dose, monthly review	
Reporting group title	S1 arm
Reporting group description:	
Standard dose, monthly review	
Reporting group title	L2 arm
Reporting group description:	
Low dose, bi-monthly review	
Reporting group title	S2 arm
Reporting group description:	
Standard dose, bi-monthly review	

Reporting group values	L1 arm	S1 arm	L2 arm
Number of subjects	204	203	203
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	8	6	4
From 65-84 years	150	143	144
85 years and over	46	54	55
Age continuous			
Age at randomisation			
Units: years			
arithmetic mean	79	80	80
standard deviation	± 7.5	± 7.6	± 7.4
Gender categorical			
Units: Subjects			
Female	120	118	118
Male	84	85	85

Reporting group values	S2 arm	Total	
Number of subjects	202	812	
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)	2	20	
From 65-84 years	139	576	
85 years and over	61	216	
Age continuous			
Age at randomisation			
Units: years			
arithmetic mean	81		
standard deviation	± 7.0	-	
Gender categorical			
Units: Subjects			
Female	109	465	
Male	93	347	

End points

End points reporting groups

Reporting group title	L1 arm
Reporting group description: Low dose, monthly review	
Reporting group title	S1 arm
Reporting group description: Standard dose, monthly review	
Reporting group title	L2 arm
Reporting group description: Low dose, bi-monthly review	
Reporting group title	S2 arm
Reporting group description: Standard dose, bi-monthly review	
Reporting group title	L1 - low dose monthly
Reporting group description: Low dose, monthly review	
Reporting group title	S1 - standard dose monthly
Reporting group description: Standard dose, monthly review	
Reporting group title	L2 - low dose bi-monthly
Reporting group description: Low dose, bi-monthly review	
Reporting group title	S2 - standard dose bi-monthly
Reporting group description: Standard dose, bi-monthly review	

Primary: Visual deterioration (VD)

End point title	Visual deterioration (VD)

End point description:

An event is visual deterioration of >=15 letters during induction compared to baseline (visit A), or >=6 letters compared to mean baseline (mean over first 3 visits A-C). Those who do not have a visual deterioration while in the study are counted as censored at the point they exit, whatever the reason for exit (died, withdrawal of consent, stable disease, end of trial, exit for VD too small to qualify). Events are counted in both primary and fellow eyes.

End point type	Primary

End point timeframe:

From randomisation (or start of treatment for late-joining fellow eyes), until exit from study.

End point values	L1 - low dose monthly	S1 - standard dose monthly	L2 - low dose bi-monthly	S2 - standard dose bi-monthly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	200[1]	200[2]	201[3]	200[4]
Units: event	62	61	83	77

Notes:

[1] - 232 eyes (primary and fellow) analysed.

[2] - 224 eyes (primary and fellow) analysed

[3] - 223 eyes (primary and fellow) analysed

[4] - 225 (primary and fellow) eyes analysed

Statistical analyses

Statistical analysis title	Cox regression analysis of primary outcome - dose

Statistical analysis description:

Cox regression analysis of time to event (VD) with shared frailty (eyes), non-inferiority. Analysis according to randomised allocation. Adjustment for centre. No interaction between dose and schedule (review interval), hence main effects of dose and schedule used for estimation. Comparison of doses and schedules (monthly vs bi-monthly) are from same analysis, but presented separately due to limitations of EudraCT reporting system.

Comparison groups	L1 - low dose monthly v S1 - standard dose monthly v L2 - low dose bi-monthly v S2 - standard dose bi-monthly
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
Parameter estimate	Cox proportional hazard
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.42

Notes:

[5] - Non-inferiority margin of 1.4. (upper 95% confidence interval for hazard ratio of less than 1.4 for non-inferiority).
Comparison of dose ie (L1+L2) vs (S1+S2)

Statistical analysis title	Cox regression for primary outcome - schedule

Statistical analysis description:

Cox regression analysis of time to event (VD) with shared frailty (eyes), non-inferiority. Analysis according to randomised allocation. Adjustment for centre. No interaction between dose and schedule (review interval), hence main effects of dose and schedule used for estimation. Comparison of doses and schedules (monthly vs bi-monthly) are from same analysis, but presented separately due to limitations of EudraCT reporting system.

Comparison groups	S1 - standard dose monthly v L2 - low dose bi-monthly v S2 - standard dose bi-monthly v L1 - low dose monthly
Number of subjects included in analysis	801
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
Parameter estimate	Cox proportional hazard
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.09
upper limit	1.94

Notes:

[6] - Non-inferiority margin of 1.4. (upper 95% confidence interval for hazard ratio of less than 1.4 for non-inferiority).
Comparison of schedule (review interval) ie (L2+S2) vs (L1+S1)

Secondary: Visual accuity (VA) at 9 months

End point title	Visual accuity (VA) at 9 months

End point description:

9 months from start of treatment with 10 week window either side. The VA reading within the window closest to 9 months will be used.

End point type	Secondary

End point timeframe:

9 months from start of treatment

End point values	L1 - low dose monthly	S1 - standard dose monthly	L2 - low dose bi-monthly	S2 - standard dose bi-monthly
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	200[7]	177[8]	182[9]	187[10]
Units: Letters read				
arithmetic mean (standard deviation)	62.4 (± 16.9)	63.9 (± 16.3)	63.5 (± 14.2)	63.4 (± 15.2)

Notes:

[7] - eyes (primary and fellow). Not all have data within time window

[8] - eyes (primary and fellow). Not all have data within time window.

[9] - eyes (primary and fellow). Not all have data within window

[10] - eyes (primary and fellow). Not all have eyes within window.

Statistical analyses

Statistical analysis title	VA at 9 months - comparison of dose

Statistical analysis description:

Mixed effects model comparing VA (visual acuity) at 9 months between doses. The model is adjusted for baseline VA score and study centre. There was no evidence of interaction between dose and schedule (review interval) hence main effects are presented. Comparison of doses and schedules (monthly vs bi-monthly) are from same analysis, but presented separately due to limitations of EudraCT reporting system.

Comparison groups	L1 - low dose monthly v S1 - standard dose monthly v L2 - low dose bi-monthly v S2 - standard dose bi-monthly
Number of subjects included in analysis	746
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	0.17

Statistical analysis title	VA at 9 months - comparison of schedule

Statistical analysis description:

Mixed effects model comparing VA (visual acuity) at 9 months between schedules (monthly vs bi-monthly). The model is adjusted for baseline VA score and study centre. There was no evidence of interaction between dose and schedule (review interval) hence main effects are presented. Comparison

of doses and schedules (monthly vs bi-monthly) are from same analysis, but presented separately due to limitations of EudraCT reporting system.

Comparison groups	L1 - low dose monthly v S1 - standard dose monthly v L2 - low dose bi-monthly v S2 - standard dose bi-monthly
Number of subjects included in analysis	746
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	1.25

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Randomisation to exit from trial.	
Adverse event reporting additional description:	
Any adverse events either observed or reported by the participant were recorded. SAEs causally related could be either possibly or probably related. A participant may have more than one SAE with outcome death, hence the total number of deaths summed from SAEs are more than the total number of deaths in the study.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15

Reporting groups	
Reporting group title	L1 (low dose, monthly review)
Reporting group description:	
Low dose, monthly review. Deaths are those occurring whilst in trial.	
Reporting group title	S1 (standard dose, monthly review)
Reporting group description:	
Standard dose, monthly review. Deaths are those occurring whilst in trial.	
Reporting group title	L2 (low dose, bi-monthly review)
Reporting group description:	
Low dose, bi-monthly review. Deaths are those occurring whilst in trial.	
Reporting group title	S2 (standard dose, bi-monthly review)
Reporting group description:	
Standard dose, bi-monthly review. Deaths are those occurring whilst in trial.	

Serious adverse events	L1 (low dose, monthly review)	S1 (standard dose, monthly review)	L2 (low dose, bi-monthly review)
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 204 (27.94%)	48 / 203 (23.65%)	49 / 203 (24.14%)
number of deaths (all causes)	11	9	8
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	16 / 204 (7.84%)	13 / 203 (6.40%)	12 / 203 (5.91%)
occurrences causally related to treatment / all	0 / 16	0 / 14	0 / 12
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 1
Vascular disorders			
Vascular disorders			

subjects affected / exposed	4 / 204 (1.96%)	5 / 203 (2.46%)	2 / 203 (0.99%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	3 / 204 (1.47%)	2 / 203 (0.99%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 4	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Reproductive system and breat disorder			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	6 / 204 (2.94%)	8 / 203 (3.94%)	7 / 203 (3.45%)
occurrences causally related to treatment / all	0 / 7	1 / 9	2 / 8
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 1
Psychiatric disorders			
Psychiatric disorder			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Investigation			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			

subjects affected / exposed	9 / 204 (4.41%)	10 / 203 (4.93%)	9 / 203 (4.43%)
occurrences causally related to treatment / all	1 / 14	1 / 11	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	7 / 204 (3.43%)	7 / 203 (3.45%)	9 / 203 (4.43%)
occurrences causally related to treatment / all	4 / 9	4 / 11	3 / 10
deaths causally related to treatment / all	0 / 1	3 / 6	0 / 2
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	6 / 204 (2.94%)	4 / 203 (1.97%)	8 / 203 (3.94%)
occurrences causally related to treatment / all	3 / 6	2 / 4	4 / 8
deaths causally related to treatment / all	0 / 1	1 / 2	0 / 1
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	2 / 204 (0.98%)	0 / 203 (0.00%)	3 / 203 (1.48%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Eye disorders			
subjects affected / exposed	4 / 204 (1.96%)	2 / 203 (0.99%)	2 / 203 (0.99%)
occurrences causally related to treatment / all	2 / 4	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	2 / 204 (0.98%)	3 / 203 (1.48%)	4 / 203 (1.97%)
occurrences causally related to treatment / all	0 / 2	1 / 4	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatobiliary disorders			

subjects affected / exposed	3 / 204 (1.47%)	2 / 203 (0.99%)	2 / 203 (0.99%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 204 (0.49%)	0 / 203 (0.00%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal and urinary disorder			
subjects affected / exposed	3 / 204 (1.47%)	3 / 203 (1.48%)	3 / 203 (1.48%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Endocrine disorders			
Endocrine disorder			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 203 (0.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculosketal and connective tissue disorder			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infections and infestations			
subjects affected / exposed	9 / 204 (4.41%)	3 / 203 (1.48%)	12 / 203 (5.91%)
occurrences causally related to treatment / all	0 / 11	1 / 4	0 / 16
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 3
Metabolism and nutrition disorders			
Metabolism and nutrition disorder			
subjects affected / exposed	0 / 204 (0.00%)	1 / 203 (0.49%)	0 / 203 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	S2 (standard dose, bi-monthly review)		
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 202 (28.71%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	15 / 202 (7.43%)		
occurrences causally related to treatment / all	0 / 15		
deaths causally related to treatment / all	0 / 3		
Vascular disorders			
Vascular disorders			
subjects affected / exposed	4 / 202 (1.98%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Reproductive system and breat disorder			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	4 / 202 (1.98%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Psychiatric disorder			

subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Investigation			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	9 / 202 (4.46%)		
occurrences causally related to treatment / all	0 / 12		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	6 / 202 (2.97%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	10 / 202 (4.95%)		
occurrences causally related to treatment / all	5 / 10		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Eye disorders			
subjects affected / exposed	2 / 202 (0.99%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	12 / 202 (5.94%)		
occurrences causally related to treatment / all	2 / 16		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal and urinary disorder			
subjects affected / exposed	1 / 202 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Endocrine disorder			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculosketal and connective tissue disorder			
subjects affected / exposed	4 / 202 (1.98%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Infections and infestations			
subjects affected / exposed	8 / 202 (3.96%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Metabolism and nutrition disorder			
subjects affected / exposed	0 / 202 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4.9 %

Non-serious adverse events	L1 (low dose, monthly review)	S1 (standard dose, monthly review)	L2 (low dose, bi-monthly review)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 204 (70.10%)	157 / 203 (77.34%)	137 / 203 (67.49%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	4 / 204 (1.96%)	7 / 203 (3.45%)	1 / 203 (0.49%)
occurrences (all)	4	10	2
Vascular disorders			
Vascular disorders			
subjects affected / exposed	10 / 204 (4.90%)	23 / 203 (11.33%)	8 / 203 (3.94%)
occurrences (all)	12	25	10
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	24 / 204 (11.76%)	36 / 203 (17.73%)	23 / 203 (11.33%)
occurrences (all)	32	43	25
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	37 / 204 (18.14%)	51 / 203 (25.12%)	23 / 203 (11.33%)
occurrences (all)	48	73	30
Immune system disorders			
Immune system disorder			

subjects affected / exposed	1 / 204 (0.49%)	3 / 203 (1.48%)	2 / 203 (0.99%)
occurrences (all)	1	3	2
Social circumstances			
Social circumstances			
subjects affected / exposed	0 / 204 (0.00%)	2 / 203 (0.99%)	0 / 203 (0.00%)
occurrences (all)	0	2	0
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	2 / 204 (0.98%)	4 / 203 (1.97%)	0 / 203 (0.00%)
occurrences (all)	3	5	0
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	18 / 204 (8.82%)	25 / 203 (12.32%)	27 / 203 (13.30%)
occurrences (all)	23	40	35
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	3 / 204 (1.47%)	8 / 203 (3.94%)	8 / 203 (3.94%)
occurrences (all)	3	8	10
Investigations			
Investigation			
subjects affected / exposed	14 / 204 (6.86%)	17 / 203 (8.37%)	12 / 203 (5.91%)
occurrences (all)	18	18	16
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	42 / 204 (20.59%)	49 / 203 (24.14%)	32 / 203 (15.76%)
occurrences (all)	65	77	44
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	12 / 204 (5.88%)	13 / 203 (6.40%)	9 / 203 (4.43%)
occurrences (all)	18	18	11
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	31 / 204 (15.20%)	43 / 203 (21.18%)	32 / 203 (15.76%)
occurrences (all)	46	56	47
Blood and lymphatic system disorders			

Blood and lymphatic system disorders			
subjects affected / exposed	5 / 204 (2.45%)	7 / 203 (3.45%)	5 / 203 (2.46%)
occurrences (all)	6	8	7
Ear and labyrinth disorders			
Ear and labyrinth disorders			
subjects affected / exposed	2 / 204 (0.98%)	10 / 203 (4.93%)	4 / 203 (1.97%)
occurrences (all)	2	10	4
Eye disorders			
Eye disorder			
subjects affected / exposed	75 / 204 (36.76%)	82 / 203 (40.39%)	67 / 203 (33.00%)
occurrences (all)	133	158	102
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	22 / 204 (10.78%)	29 / 203 (14.29%)	24 / 203 (11.82%)
occurrences (all)	35	40	32
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	1 / 204 (0.49%)	1 / 203 (0.49%)	1 / 203 (0.49%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	11 / 204 (5.39%)	12 / 203 (5.91%)	13 / 203 (6.40%)
occurrences (all)	11	15	15
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	7 / 204 (3.43%)	6 / 203 (2.96%)	9 / 203 (4.43%)
occurrences (all)	8	6	10
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	0 / 204 (0.00%)	0 / 203 (0.00%)	1 / 203 (0.49%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	26 / 204 (12.75%)	26 / 203 (12.81%)	20 / 203 (9.85%)
occurrences (all)	36	31	25
Infections and infestations			

Infections and infestations subjects affected / exposed occurrences (all)	52 / 204 (25.49%) 85	58 / 203 (28.57%) 108	48 / 203 (23.65%) 78
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	10 / 204 (4.90%) 11	6 / 203 (2.96%) 8	4 / 203 (1.97%) 4

Non-serious adverse events	S2 (standard dose, bi-monthly review)		
Total subjects affected by non-serious adverse events subjects affected / exposed	141 / 202 (69.80%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Neoplasms benign, malignant and unspecified (incl cysts and polyps) subjects affected / exposed occurrences (all)	3 / 202 (1.49%) 4		
Vascular disorders Vascular disorders subjects affected / exposed occurrences (all)	11 / 202 (5.45%) 14		
Surgical and medical procedures Surgical and medical procedures subjects affected / exposed occurrences (all)	32 / 202 (15.84%) 41		
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	26 / 202 (12.87%) 27		
Immune system disorders Immune system disorder subjects affected / exposed occurrences (all)	2 / 202 (0.99%) 2		
Social circumstances Social circumstances subjects affected / exposed occurrences (all)	0 / 202 (0.00%) 0		
Reproductive system and breast disorders			

Reproductive system and breast disorders subjects affected / exposed occurrences (all)	3 / 202 (1.49%) 3		
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	20 / 202 (9.90%) 31		
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	3 / 202 (1.49%) 3		
Investigations Investigation subjects affected / exposed occurrences (all)	9 / 202 (4.46%) 11		
Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all)	33 / 202 (16.34%) 55		
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	14 / 202 (6.93%) 16		
Nervous system disorders Nervous system disorder subjects affected / exposed occurrences (all)	36 / 202 (17.82%) 46		
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	4 / 202 (1.98%) 4		
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	2 / 202 (0.99%) 2		
Eye disorders			

Eye disorder subjects affected / exposed occurrences (all)	57 / 202 (28.22%) 88		
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	16 / 202 (7.92%) 32		
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	2 / 202 (0.99%) 2		
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	8 / 202 (3.96%) 8		
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	2 / 202 (0.99%) 2		
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	2 / 202 (0.99%) 4		
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	18 / 202 (8.91%) 20		
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	49 / 202 (24.26%) 86		
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	6 / 202 (2.97%) 7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2010	1. Sample size calculations were not consistent across the protocol. Changes resulted in changes to inclusion/exclusion 2. Additional expected ocular and non-ocular AEs/SAEs 3. The sponsor to retain responsibility for the reporting of SUSARs to the authorities 4. Sites in Sherwood Forest and Kettering have a change in Principal Investigator 5. Northampton General Hospital, Chesterfield Royal Hospital and Leicester Royal Infirmary no longer participating in the study 6. Replacement of patient representative from the Macular Disease Society 7. Minor re-wording of the Patient Information Sheet
06 April 2011	Changes are required to the protocol to include DNA testing for patients who are randomised to the study. Observational patients are being included in the study. Changes are also required to the initial application to the REC and MHRA on confidentiality Changes to patient information sheet and consent form. Inclusion of Leicester as a site.
29 November 2011	The background section has been updated with new scientific evidence. Changes have also been made to: - comply with Sponsor's template. - the description of eligibility and review of patients with respect to criteria of withdrawal from the trial. DNA testing for patients who are randomised to the study has been removed. Patient Information Sheet, Patient Consent Form, Patient Health Record, Patient Study Card, TANDEM Poster, Post injection sheet updated
15 May 2012	The protocol reflects the following changes: Move from Bristol Coordinating Centre to Nottingham Clinical Trials Unit. Removal of observational study Patient information sheet, patient card and poster also amended
13 September 2013	Safety section (reporting procedures) updated following MHRA inspection visit of 30th July 2013. Change of statistician Update of DMC wording to reflect role and remit within the trial.
13 January 2015	Minor wording amendments made to: 11.2.1 'SAE Reporting'- reporting timeframe has been clarified. 13.1 'Proposed actions to comply with 'The Medicines for Human Use (Clinical Trials) Regulations 2004': Update of wording to reflect Sponsor audit procedure Addition of new references.
25 November 2015	Minor wording clarifications made to: Protocol synopsis; study drug low dose weight amended 4.3 Participating centres; PCTs amended to CCGs 5.1.3 Unmasking Procedure now referenced Formatting applied throughout protocol Derby centre closed. The Patient Information Sheet updated to reflect the use of Eyelea® for wAMD in standard NHS practice.

11 May 2016	Removal of the interim analysis Changes to reflect the transfer of Serious Adverse Events and Deviation reporting from the sponsor (Nottingham University Hospitals Research and Innovation) to the Nottingham Clinical Trials Unit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 December 2011	Temporary suspension due to move from Bristol to Nottingham coordinating centre, modification of baseline data collection and database. Dates are of substantial amendments. The last randomisation prior to suspension was 18-Nov-2011; the first after suspension was 30-Jul-2012.	15 May 2012

Notes:

Limitations and caveats

None reported