



## Clinical trial results:

### A Phase II Randomized Study to Compare Anti-VEGF Agents in the Treatment of Diabetic Macular Edema (CADME)

#### Summary

EudraCT number	2012-005486-13
Trial protocol	GB
Global end of trial date	15 July 2015

#### Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016
Summary attachment (see zip file)	CADME Study Final Results (Crossover Design for Comparative Efficacy_AAO 2016.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	12-EI-0134
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01610557
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	National Eye Institute
Sponsor organisation address	NIH , Bethesda, United States,
Public contact	Henry Wiley, National Eye Institute, wileyhe@nei.nih.gov
Scientific contact	Henry Wiley, National Eye Institute, wileyhe@nei.nih.gov

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	09 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 July 2015
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

The main study objective was to compare the treatment efficacy of ranibizumab versus bevacizumab in eyes with diabetic macular edema (DME).

Protection of trial subjects:

Institutional review board/independent ethics committee approval was obtained at both sites and all participants gave written informed consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	56
EEA total number of subjects	41

Notes:

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**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)	33
From 65 to 84 years	21
85 years and over	2

## Subject disposition

### Recruitment

Recruitment details:

Eligible participants had type 1 or type 2 diabetes mellitus, were at least 18 years old, and could enter one or both eligible eyes in the study.

### Pre-assignment

Screening details:

56 participants enrolled: 50 participants had one eye randomly assigned (unilateral participants) and 6 participants had two eyes enrolled (bilateral participants) for a total of 62 eyes analyzed at baseline. Bilateral participants had the right eye randomly assigned and the left eye assigned to the group with the schedule inverse to the right eye.

### Period 1

Period 1 title	36-Week Randomized Crossover Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Participants were assigned to one of the four treatment sequences using a randomization list generated by the Data and Statistical Coordinating Center prior to study initiation, with balance following every 12 enrollments. The list was provided to unmasked pharmacists at each site who confirmed a valid participant identification code prior to dispensing study treatment. Both clinical sites utilized the same randomized list, but selected treatment assignments from opposite ends.

### Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1 - Ranibizumab-Ranibizumab-Bevacizumab Injection Series

Arm description:

Group 1 eyes were assigned to the Ranibizumab-Ranibizumab-Bevacizumab (RRB) treatment sequence and received intravitreal injections of ranibizumab at baseline, Weeks 4, and 8 (period 1), and Weeks 12, 16 and 20 (period 2), then crossed over to receive intravitreal injections of bevacizumab at Weeks 24, 28 and 32 (period 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 1: 14 unilateral and 2 bilateral (left eye assigned to Group 3)  
Participants' eyes assigned to Group 1: 17

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

**Dosage and administration details:**

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

<b>Arm title</b>	Group 2 - Ranibizumab-Bevacizumab-Bevacizumab Injection Series
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**Arm description:**

Group 2 eyes were assigned to the Ranibizumab-Bevacizumab-Bevacizumab (RBB) treatment sequence and received intravitreal injections of ranibizumab at baseline and Weeks 4 and 8 (period 1), then crossed over to receive intravitreal injections of bevacizumab at Weeks 12, 16, 20, 24, 28 and 32 (periods 2 and 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 2: 12 unilateral and 1 bilateral (left eye assigned to Group 4)  
Participants' eyes assigned to Group 2: 15

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

**Dosage and administration details:**

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

**Dosage and administration details:**

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study

(98% of all injections).

<b>Arm title</b>	Group 3 - Bevacizumab-Bevacizumab-Ranibizumab Injection Series
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**Arm description:**

Group 3 eyes were assigned to the Bevacizumab-Bevacizumab-Ranibizumab (BBR) treatment sequence and received intravitreal injections of bevacizumab at baseline and Weeks 4, 8, 12, 16 and 20 (periods 1 and 2), then crossed over to receive intravitreal injections of ranibizumab at Weeks 24, 28 and 32 (period 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 3: 13 unilateral and 1 bilateral (left eye assigned to Group 1)  
Participants' eyes assigned to Group 3: 16

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

**Dosage and administration details:**

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

**Dosage and administration details:**

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

<b>Arm title</b>	Group 4 - Bevacizumab-Ranibizumab-Ranibizumab Injection Series
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**Arm description:**

Group 4 eyes were assigned to the Bevacizumab-Ranibizumab-Ranibizumab (BRR) treatment sequence and received intravitreal injections of bevacizumab at baseline and Weeks 4 and 8 (period 1), then crossed over to receive intravitreal injections of ranibizumab at Weeks 12, 16, 20, 24, 28 and 32 (periods 2 and 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled

(bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 4: 11 unilateral and 2 bilateral (left eye assigned to Group 2)  
Participants' eyes assigned to Group 4: 14

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

<b>Number of subjects in period 1</b>	Group 1 - Ranibizumab- Ranibizumab- Bevacizumab Injection Series	Group 2 - Ranibizumab- Bevacizumab- Bevacizumab Injection Series	Group 3 - Bevacizumab- Bevacizumab- Ranibizumab Injection Series
Started	16	13	14
Completed	16	12	14
Not completed	0	1	0
Consent withdrawn by subject	-	1	-

<b>Number of subjects in period 1</b>	Group 4 - Bevacizumab- Ranibizumab- Ranibizumab Injection Series
Started	13

Completed	13
Not completed	0
Consent withdrawn by subject	-

## Period 2

Period 2 title	Post-36-Week Extension Phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

## Arms

<b>Arm title</b>	Ranibizumab/Bevacizumab As Needed
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### Arm description:

Post-36-Week Extension Phase: Eyes assigned to Group 1 or Group 2 in the crossover phase were injected with ranibizumab on an as-needed basis. Eyes assigned to Group 3 or Group 4 in the crossover phase were injected with bevacizumab on an as-needed basis.

53 participants attended at least one follow-up visit in the post-36-week extension phase: 49 participants who had one eye enrolled and 4 participants who had two eyes enrolled. Two bilateral participants withdrew before their first post-36-week extension visit

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

### Dosage and administration details:

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

### Dosage and administration details:

Series of three intravitreal injections of ranibizumab [0.3 milligrams (mg)]\* or bevacizumab (1.25 mg) administered every 4 weeks for three 12-week periods. Following this crossover phase, eyes received ranibizumab or bevacizumab to which they were originally assigned and treated on an as-needed basis until study completion.

\*Eleven doses of ranibizumab 0.5 mg were given to participants at the start of the study; after the United States (US) Food and Drug Administration (FDA) approval of the 0.3 mg dose for diabetic

macular edema (DME), the protocol was amended and 0.3 mg was used for the remainder of the study (98% of all injections).

<b>Number of subjects in period 2</b>	Ranibizumab/Bevacizumab As Needed
Started	55
Completed	52
Not completed	3
Consent withdrawn by subject	3



## Baseline characteristics

### Reporting groups

Reporting group title	Group 1 - Ranibizumab-Ranibizumab-Bevacizumab Injection Series
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#### Reporting group description:

Group 1 eyes were assigned to the Ranibizumab-Ranibizumab-Bevacizumab (RRB) treatment sequence and received intravitreal injections of ranibizumab at baseline, Weeks 4, and 8 (period 1), and Weeks 12, 16 and 20 (period 2), then crossed over to receive intravitreal injections of bevacizumab at Weeks 24, 28 and 32 (period 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 1: 14 unilateral and 2 bilateral (left eye assigned to Group 3)  
Participants' eyes assigned to Group 1: 17

Reporting group title	Group 2 - Ranibizumab-Bevacizumab-Bevacizumab Injection Series
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#### Reporting group description:

Group 2 eyes were assigned to the Ranibizumab-Bevacizumab-Bevacizumab (RBB) treatment sequence and received intravitreal injections of ranibizumab at baseline and Weeks 4 and 8 (period 1), then crossed over to receive intravitreal injections of bevacizumab at Weeks 12, 16, 20, 24, 28 and 32 (periods 2 and 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 2: 12 unilateral and 1 bilateral (left eye assigned to Group 4)  
Participants' eyes assigned to Group 2: 15

Reporting group title	Group 3 - Bevacizumab-Bevacizumab-Ranibizumab Injection Series
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#### Reporting group description:

Group 3 eyes were assigned to the Bevacizumab-Bevacizumab-Ranibizumab (BBR) treatment sequence and received intravitreal injections of bevacizumab at baseline and Weeks 4, 8, 12, 16 and 20 (periods 1 and 2), then crossed over to receive intravitreal injections of ranibizumab at Weeks 24, 28 and 32 (period 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 3: 13 unilateral and 1 bilateral (left eye assigned to Group 1)  
Participants' eyes assigned to Group 3: 16

Reporting group title	Group 4 - Bevacizumab-Ranibizumab-Ranibizumab Injection Series
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#### Reporting group description:

Group 4 eyes were assigned to the Bevacizumab-Ranibizumab-Ranibizumab (BRR) treatment sequence and received intravitreal injections of bevacizumab at baseline and Weeks 4 and 8 (period 1), then crossed over to receive intravitreal injections of ranibizumab at Weeks 12, 16, 20, 24, 28 and 32 (periods 2 and 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 4: 11 unilateral and 2 bilateral (left eye assigned to Group 2)  
Participants' eyes assigned to Group 4: 14

Reporting group values	Group 1 - Ranibizumab- Ranibizumab- Bevacizumab Injection Series	Group 2 - Ranibizumab- Bevacizumab- Bevacizumab Injection Series	Group 3 - Bevacizumab- Bevacizumab- Ranibizumab Injection Series
Number of subjects	16	13	14

Age categorical			
Units: Subjects			
Age continuous			
Participants with both eyes enrolled are counted twice (by eye), once for each of the treatment sequences to which an eye was assigned randomly. Although 56 participants enrolled, 6 participants had two eyes enrolled for a total of 62 eyes. This age baseline characteristic reflects the number of eyes enrolled in each group: Group 1 had 17 eyes enrolled, Group 2 had 15 eyes enrolled, Group 3 had 16 eyes enrolled and Group 4 had 14 eyes enrolled.			
Units: years			
arithmetic mean	62.4	65.9	62.3
full range (min-max)	39 to 85	39 to 87	39 to 83
Gender categorical			
The gender baseline characteristic reflects the number of participants enrolled rather than the number of eyes enrolled.			
Units: Subjects			
Female	3	7	7
Male	13	6	7

<b>Reporting group values</b>	Group 4 - Bevacizumab- Ranibizumab- Ranibizumab Injection Series	Total	
Number of subjects	13	56	
Age categorical			
Units: Subjects			

Age continuous			
Participants with both eyes enrolled are counted twice (by eye), once for each of the treatment sequences to which an eye was assigned randomly. Although 56 participants enrolled, 6 participants had two eyes enrolled for a total of 62 eyes. This age baseline characteristic reflects the number of eyes enrolled in each group: Group 1 had 17 eyes enrolled, Group 2 had 15 eyes enrolled, Group 3 had 16 eyes enrolled and Group 4 had 14 eyes enrolled.			
Units: years			
arithmetic mean	61.8		
full range (min-max)	51 to 82	-	
Gender categorical			
The gender baseline characteristic reflects the number of participants enrolled rather than the number of eyes enrolled.			
Units: Subjects			
Female	4	21	
Male	9	35	

## Subject analysis sets

Subject analysis set title	Ranibizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Represents the estimated effect of ranibizumab for a 3-month period, adjusted for period and baseline value. A total of 56 participants (62 eyes) were enrolled and 55 participants (61 eyes) completed the 36-week crossover phase of the study.	
Subject analysis set title	Bevacizumab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Represents the estimated effect of bevacizumab for a 3-month period, adjusted for period and baseline	

value. A total of 56 participants (62 eyes) were enrolled and 55 participants (61 eyes) completed the 36-week crossover phase of the study.

Reporting group values	Ranibizumab	Bevacizumab	
Number of subjects	55	55	
Age categorical			
Units: Subjects			
Age continuous			
Participants with both eyes enrolled are counted twice (by eye), once for each of the treatment sequences to which an eye was assigned randomly. Although 56 participants enrolled, 6 participants had two eyes enrolled for a total of 62 eyes. This age baseline characteristic reflects the number of eyes enrolled in each group: Group 1 had 17 eyes enrolled, Group 2 had 15 eyes enrolled, Group 3 had 16 eyes enrolled and Group 4 had 14 eyes enrolled.			
Units: years			
arithmetic mean			
full range (min-max)			
Gender categorical			
The gender baseline characteristic reflects the number of participants enrolled rather than the number of eyes enrolled.			
Units: Subjects			
Female	21	21	
Male	34	34	

## End points

### End points reporting groups

Reporting group title	Group 1 - Ranibizumab-Ranibizumab-Bevacizumab Injection Series
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#### Reporting group description:

Group 1 eyes were assigned to the Ranibizumab-Ranibizumab-Bevacizumab (RRB) treatment sequence and received intravitreal injections of ranibizumab at baseline, Weeks 4, and 8 (period 1), and Weeks 12, 16 and 20 (period 2), then crossed over to receive intravitreal injections of bevacizumab at Weeks 24, 28 and 32 (period 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 1: 14 unilateral and 2 bilateral (left eye assigned to Group 3)  
Participants' eyes assigned to Group 1: 17

Reporting group title	Group 2 - Ranibizumab-Bevacizumab-Bevacizumab Injection Series
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#### Reporting group description:

Group 2 eyes were assigned to the Ranibizumab-Bevacizumab-Bevacizumab (RBB) treatment sequence and received intravitreal injections of ranibizumab at baseline and Weeks 4 and 8 (period 1), then crossed over to receive intravitreal injections of bevacizumab at Weeks 12, 16, 20, 24, 28 and 32 (periods 2 and 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 2: 12 unilateral and 1 bilateral (left eye assigned to Group 4)  
Participants' eyes assigned to Group 2: 15

Reporting group title	Group 3 - Bevacizumab-Bevacizumab-Ranibizumab Injection Series
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#### Reporting group description:

Group 3 eyes were assigned to the Bevacizumab-Bevacizumab-Ranibizumab (BBR) treatment sequence and received intravitreal injections of bevacizumab at baseline and Weeks 4, 8, 12, 16 and 20 (periods 1 and 2), then crossed over to receive intravitreal injections of ranibizumab at Weeks 24, 28 and 32 (period 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 3: 13 unilateral and 1 bilateral (left eye assigned to Group 1)  
Participants' eyes assigned to Group 3: 16

Reporting group title	Group 4 - Bevacizumab-Ranibizumab-Ranibizumab Injection Series
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#### Reporting group description:

Group 4 eyes were assigned to the Bevacizumab-Ranibizumab-Ranibizumab (BRR) treatment sequence and received intravitreal injections of bevacizumab at baseline and Weeks 4 and 8 (period 1), then crossed over to receive intravitreal injections of ranibizumab at Weeks 12, 16, 20, 24, 28 and 32 (periods 2 and 3). Participants for whom one eye was enrolled (unilateral participants) in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled (bilateral participants) had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 4: 11 unilateral and 2 bilateral (left eye assigned to Group 2)  
Participants' eyes assigned to Group 4: 14

Reporting group title	Ranibizumab/Bevacizumab As Needed
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#### Reporting group description:

Post-36-Week Extension Phase: Eyes assigned to Group 1 or Group 2 in the crossover phase were injected with ranibizumab on an as-needed basis. Eyes assigned to Group 3 or Group 4 in the crossover phase were injected with bevacizumab on an as-needed basis.

53 participants attended at least one follow-up visit in the post-36-week extension phase: 49 participants who had one eye enrolled and 4 participants who had two eyes enrolled. Two bilateral

Subject analysis set title	Ranibizumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Represents the estimated effect of ranibizumab for a 3-month period, adjusted for period and baseline value. A total of 56 participants (62 eyes) were enrolled and 55 participants (61 eyes) completed the 36-week crossover phase of the study.

Subject analysis set title	Bevacizumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Represents the estimated effect of bevacizumab for a 3-month period, adjusted for period and baseline value. A total of 56 participants (62 eyes) were enrolled and 55 participants (61 eyes) completed the 36-week crossover phase of the study.

## Primary: Mean Change in Early Treatment Diabetic Retinopathy Study (ETDRS) Best-corrected Visual Acuity (BCVA) From Baseline to 36 Weeks (Crossover Phase of the Study)

End point title	Mean Change in Early Treatment Diabetic Retinopathy Study (ETDRS) Best-corrected Visual Acuity (BCVA) From Baseline to 36 Weeks (Crossover Phase of the Study)
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End point description:

The primary outcome for 3-months change in BCVA utilized data from Weeks 12, 24 and 36 aggregated in a linear mixed-effects model. This model included adjustments accounting for period (i.e., Weeks 12, 24 and 36), treatment in current period, treatment in prior period, and baseline BCVA to provide the estimated 3-month BCVA change. A positive change from baseline indicated improvement.

Visual acuity was measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. Acuity is measured as letters read on an ETDRS eye chart and the letters read equate to Snellen measurements. For example, if a participant reads between 84 and 88 letters, the equivalent Snellen measurement is 20/20.

End point type	Primary
End point timeframe:	Baseline, 36 Weeks

End point values	Ranibizumab	Bevacizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55 <sup>[1]</sup>	55 <sup>[2]</sup>		
Units: ETDRS letters				
arithmetic mean (confidence interval 95%)	5.3 (3.2 to 7.4)	6.6 (4.5 to 8.7)		

Notes:

[1] - The total number of eyes included in the analysis is 61.

[2] - The total number of eyes included in the analysis is 61.

## Statistical analyses

Statistical analysis title	Ranibizumab versus Bevacizumab
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Statistical analysis description:

The comparison groups are ranibizumab and bevacizumab with a total of 55 participants (61 eyes) included in the analysis. The difference represents the estimated difference between ranibizumab and bevacizumab, adjusted for baseline visual acuity, study period, and clinical site and a subject effect for eyes nested within subject.

Comparison groups	Ranibizumab v Bevacizumab
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Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.039
Method	Linear mixed-effects model
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	2.5

### Secondary: Change in Central Retinal Thickness Assessed by Optical Coherence Tomography (OCT) Central Subfield Mean Thickness (CSMT) From Baseline to 36 Weeks (Crossover Phase of the Study)

End point title	Change in Central Retinal Thickness Assessed by Optical Coherence Tomography (OCT) Central Subfield Mean Thickness (CSMT) From Baseline to 36 Weeks (Crossover Phase of the Study)
End point description:	Optical Coherence Tomography (OCT) scans were graded in masked fashion by Duke University Reading Center (Durham, North Carolina). Per the initial protocol specifications, OCT scans were to be performed on a Cirrus OCT machine; however, some scans were performed on a Spectralis OCT machine at one of the sites due to technical difficulties. The protocol was amended to allow for Cirrus and Spectralis OCT scans at subsequent visits at the affected site. Spectralis values were then converted to Cirrus central subfield mean thickness (CSMT) values through a validated linear conversion function. A negative change from baseline indicates improvement.
End point type	Secondary
End point timeframe:	Baseline, 36 Weeks

End point values	Ranibizumab	Bevacizumab		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55 <sup>[3]</sup>	55 <sup>[4]</sup>		
Units: micrometers				
arithmetic mean (confidence interval 95%)	-89 (-116 to -62)	-137 (-164 to -110)		

Notes:

[3] - The total number of eyes included in the analysis is 61.

[4] - The total number of eyes included in the analysis is 61.

### Statistical analyses

Statistical analysis title	Ranibizumab versus Bevacizumab
Statistical analysis description:	The comparison groups are ranibizumab and bevacizumab with a total of 55 participants (61 eyes) included in the analysis.
Comparison groups	Ranibizumab v Bevacizumab

Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Linear mixed-effects model
Parameter estimate	Mean difference (final values)
Point estimate	-48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65
upper limit	-31

## Adverse events

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### Adverse events information

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Timeframe for reporting adverse events:

Data were collected from 56 participants randomly-assigned to Groups 1 through 4 during the 36-week crossover period. After 36 weeks, data were collected from the 53 participants who completed at least one post-36-week visit up to the termination visit.

Adverse event reporting additional description:

36-week crossover period: Of the 56 participants, 50 had one eye and 6 had two eyes enrolled; data collected from the 6 participants with two eyes enrolled are reflected in the group to which the participant's right eye was randomly assigned. Post-36-weeks: Of the 53 participants, data were collected from 49 with one eye and 4 with two eyes enrolled.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	15.0-17.1

### Reporting groups

Reporting group title	Group 1 - Ranibizumab-Ranibizumab-Bevacizumab Injection Series
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Reporting group description:

Group 1 eyes were assigned to the Ranibizumab-Ranibizumab-Bevacizumab (RRB) treatment sequence and received intravitreal injections of ranibizumab at baseline, Weeks 4, and 8 (period 1), and Weeks 12, 16 and 20 (period 2), then crossed over to receive intravitreal injections of bevacizumab at Weeks 24, 28 and 32 (period 3). Participants for whom one eye was enrolled in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 1: 14 unilateral and 2 bilateral (left eye assigned to Group 3)

Reporting group title	Group 2 - Ranibizumab-Bevacizumab-Bevacizumab Injection Series
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Reporting group description:

Group 2 eyes were assigned to the Ranibizumab-Bevacizumab-Bevacizumab (RBB) treatment sequence and received intravitreal injections of ranibizumab at baseline and Weeks 4 and 8 (period 1), then crossed over to receive intravitreal injections of bevacizumab at Weeks 12, 16, 20, 24, 28 and 32 (periods 2 and 3). Participants for whom one eye was enrolled in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 2: 12 unilateral and 1 bilateral (left eye assigned to Group 4)

Reporting group title	Group 3 - Bevacizumab-Bevacizumab-Ranibizumab Injection Series
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Reporting group description:

Group 3 eyes were assigned to the Bevacizumab-Bevacizumab-Ranibizumab (BBR) treatment sequence and received intravitreal injections of bevacizumab at baseline and Weeks 4, 8, 12, 16 and 20 (periods 1 and 2), then crossed over to receive intravitreal injections of ranibizumab at Weeks 24, 28 and 32 (period 3). Participants for whom one eye was enrolled in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled had the right eye randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Participants randomly assigned to Group 3: 13 unilateral and 1 bilateral (left eye assigned to Group 1)

Reporting group title	Group 4 - Bevacizumab-Ranibizumab-Ranibizumab Injection Series
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Reporting group description:

Group 4 eyes were assigned to the Bevacizumab-Ranibizumab-Ranibizumab (BRR) treatment sequence and received intravitreal injections of bevacizumab at baseline and Weeks 4 and 8 (period 1), then crossed over to receive intravitreal injections of ranibizumab at Weeks 12, 16, 20, 24, 28 and 32 (periods 2 and 3). Participants for whom one eye was enrolled in the study had this eye randomly assigned to one of four groups. Participants for whom both eyes were enrolled had the right eye



randomly assigned; the left eye was assigned to the group with the schedule inverse to that for the right eye.

Reporting group title	Ranibizumab As Needed (Post-36-Week Extension)
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Reporting group description:

Post-36-Week Extension Phase: Eyes assigned to Group 1 or Group 2 in the crossover phase were injected with ranibizumab on an as-needed basis.

Participants with one eye assigned in either Group 1 or Group 2 who had at least one follow-up visit in the post-36-week extension are included in the number of participants at risk.

Participants for whom two eyes were assigned (bilateral participants) are not included.

Reporting group title	Bevacizumab As Needed (Post-36-Week Extension)
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Reporting group description:

Post-36-Week Extension Phase: Eyes assigned to Group 3 or Group 4 in the crossover phase were injected with bevacizumab on an as-needed basis.

Participants with one eye assigned in either Group 3 or Group 4 who had at least one follow-up visit in the post-36-week extension are included in the number of participants at risk.

Participants for whom two eyes were assigned (bilateral participants) are not included.

Reporting group title	Ranibizumab and Bevacizumab As Needed (Post-36-Week Extension)
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Reporting group description:

Post-36-Week Extension Phase: Eyes assigned to Group 1 or Group 2 in the crossover phase were injected with ranibizumab on an as-needed basis. Eyes assigned to Group 3 or Group 4 in the crossover phase were injected with bevacizumab on an as-needed basis.

Participants with two eyes assigned who had at least one follow-up visit in the post-36-week extension are included in the number of participants at risk.

Participants for whom one eye was assigned (unilateral participants) are not included.

<b>Serious adverse events</b>	Group 1 - Ranibizumab- Ranibizumab- Bevacizumab Injection Series	Group 2 - Ranibizumab- Bevacizumab- Bevacizumab Injection Series	Group 3 - Bevacizumab- Bevacizumab- Ranibizumab Injection Series
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 16 (18.75%)	1 / 13 (7.69%)	1 / 14 (7.14%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (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
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	1 / 14 (7.14%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders	Cerebral haemorrhage			
	subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	0 / 14 (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
Syncope	subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	1 / 14 (7.14%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders	Cholecystitis			
	subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (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
Infections and infestations	Cellulitis			
	subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	1 / 14 (7.14%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection	subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis	subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (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
Pneumonia	subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
	occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Serious adverse events</b>		Group 4 - Bevacizumab- Ranibizumab- Ranibizumab Injection Series	Ranibizumab As Needed (Post-36- Week Extension)	Bevacizumab As Needed (Post-36- Week Extension)

Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	1 / 25 (4.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			

subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	0 / 24 (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
<b>Osteomyelitis</b>			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Pneumonia</b>			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (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

<b>Serious adverse events</b>	Ranibizumab and Bevacizumab As Needed (Post-36-Week Extension)		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
<b>Investigations</b>			
Blood glucose increased			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Cardiac disorders</b>			
Arrhythmia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
<b>Nervous system disorders</b>			
Cerebral haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 4 (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: 5 %

<b>Non-serious adverse events</b>	Group 1 - Ranibizumab- Ranibizumab- Bevacizumab Injection Series	Group 2 - Ranibizumab- Bevacizumab- Bevacizumab Injection Series	Group 3 - Bevacizumab- Bevacizumab- Ranibizumab Injection Series
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 16 (81.25%)	12 / 13 (92.31%)	9 / 14 (64.29%)
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Hypotension subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Surgical and medical procedures Cyst removal subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 13 (7.69%) 1	0 / 14 (0.00%) 0
General disorders and administration site conditions Adverse drug reaction subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Chest pain subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Malaise subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Peripheral swelling subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 13 (7.69%) 1	0 / 14 (0.00%) 0

Hypersensitivity subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Reproductive system and breast disorders Breast mass subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)  Cough subjects affected / exposed occurrences (all)  Epistaxis subjects affected / exposed occurrences (all)  Sinus congestion subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0  0 / 16 (0.00%) 0  0 / 16 (0.00%) 0  0 / 16 (0.00%) 0	0 / 13 (0.00%) 0  1 / 13 (7.69%) 1  0 / 13 (0.00%) 0  0 / 13 (0.00%) 0	1 / 14 (7.14%) 1  0 / 14 (0.00%) 0  1 / 14 (7.14%) 1  0 / 14 (0.00%) 0
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)  Depressed mood subjects affected / exposed occurrences (all)  Depression subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0  1 / 16 (6.25%) 1  0 / 16 (0.00%) 0	0 / 13 (0.00%) 0  0 / 13 (0.00%) 0  1 / 13 (7.69%) 1	0 / 14 (0.00%) 0  0 / 14 (0.00%) 0  0 / 14 (0.00%) 0
Investigations Albumin urine present subjects affected / exposed occurrences (all)  Blood iron decreased	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Intraocular pressure increased subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Injury, poisoning and procedural complications			
Chest injury subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Corneal abrasion subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 2	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Procedural nausea subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Stress fracture subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Wound subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Wrist fracture subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Cardiac disorders			
Cardiac failure congestive subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Nervous system disorders			



Diabetic neuropathy subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Hyposmia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
IIIrd nerve paralysis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
IVth nerve paralysis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 13 (7.69%) 1	0 / 14 (0.00%) 0
Sciatica subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Subarachnoid haemorrhage subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
VIIth nerve paralysis subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Eye disorders Blepharitis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 13 (7.69%) 2	1 / 14 (7.14%) 2
Blepharospasm subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Cataract			

subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 16 (0.00%)	2 / 13 (15.38%)	2 / 14 (14.29%)
occurrences (all)	0	2	2
Conjunctivitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Corneal erosion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Eye pain			
subjects affected / exposed	2 / 16 (12.50%)	2 / 13 (15.38%)	0 / 14 (0.00%)
occurrences (all)	2	2	0
Eye pruritis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Eyelid oedema			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Lenticular opacities			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Posterior capsule opacification			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Retinal haemorrhage			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	0 / 16 (0.00%)	2 / 13 (15.38%)	0 / 14 (0.00%)
occurrences (all)	0	3	0
Vitreous haematoma			

subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Vitreous detachment subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Vitreous haemorrhage subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Colitis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 13 (7.69%) 1	0 / 14 (0.00%) 0
Tongue ulceration subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Hepatobiliary disorders			
Early satiety subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Hepatic cirrhosis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Skin and subcutaneous tissue disorders			

Blister			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Dermatitis contact			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 16 (12.50%)	0 / 13 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	1
Back pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Cellulitis			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Influenza			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Localised infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 16 (0.00%)	1 / 13 (7.69%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Otitis media			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 16 (0.00%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	1 / 16 (6.25%)	0 / 13 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0

Tonsillitis subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Viral infection subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Metabolism and nutrition disorders			
Dehydration subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Gout subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 13 (0.00%) 0	1 / 14 (7.14%) 1
Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	0 / 13 (0.00%) 0	0 / 14 (0.00%) 0

<b>Non-serious adverse events</b>	Group 4 - Bevacizumab- Ranibizumab- Ranibizumab Injection Series	Ranibizumab As Needed (Post-36- Week Extension)	Bevacizumab As Needed (Post-36- Week Extension)
Total subjects affected by non-serious adverse events subjects affected / exposed	9 / 13 (69.23%)	13 / 25 (52.00%)	12 / 24 (50.00%)
Vascular disorders			
Hypertension subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Hypotension subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	1 / 24 (4.17%) 2
Surgical and medical procedures			

Cyst removal subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
General disorders and administration site conditions			
Adverse drug reaction subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Chest pain subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Influenza like illness subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	2 / 24 (8.33%) 2
Malaise subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Oedema peripheral subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 25 (4.00%) 1	0 / 24 (0.00%) 0
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 2	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Immune system disorders			
Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Hypersensitivity subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Reproductive system and breast disorders			
Breast mass subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0

Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Sinus congestion			
subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Depressed mood			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Depression			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Investigations			
Albumin urine present			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Blood iron decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Intraocular pressure increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1



Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Corneal abrasion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Fall			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Procedural nausea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Stress fracture			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Wrist fracture			
subjects affected / exposed	2 / 13 (15.38%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hyposmia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0

IIIrd nerve paralysis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
IVth nerve paralysis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Sciatica subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Subarachnoid haemorrhage subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
VIIth nerve paralysis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Eye disorders Blepharitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 2	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Blepharospasm subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Cataract subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	1 / 24 (4.17%) 1
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Corneal erosion			

subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Eye pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Eye pruritis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Lenticular opacities			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Posterior capsule opacification			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Retinal haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Vitreous haematoma			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Vitreous detachment			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Vitreous haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	3 / 24 (12.50%)
occurrences (all)	0	0	4
Gastrointestinal disorders			

Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 25 (4.00%) 1	0 / 24 (0.00%) 0
Colitis subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Constipation subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	2 / 24 (8.33%) 2
Diarrhoea subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 25 (4.00%) 1	0 / 24 (0.00%) 0
Tongue ulceration subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Hepatobiliary disorders Early satiety subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Hepatic cirrhosis subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	1 / 24 (4.17%) 1
Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Dermatitis contact subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Skin lesion			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	1 / 24 (4.17%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	2 / 13 (15.38%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Myalgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Rheumatoid arthritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Ear infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	1 / 13 (7.69%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences (all)	1	0	1
Influenza			

subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Localised infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	3 / 13 (23.08%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	3	1	0
Otitis media			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Tonsillitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	2 / 24 (8.33%)
occurrences (all)	0	1	2
Viral infection			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 25 (0.00%) 0	0 / 24 (0.00%) 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Gout			
subjects affected / exposed	0 / 13 (0.00%)	0 / 25 (0.00%)	0 / 24 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 25 (4.00%)	0 / 24 (0.00%)
occurrences (all)	0	1	0

<b>Non-serious adverse events</b>	Ranibizumab and Bevacizumab As Needed (Post-36-Week Extension)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Cyst removal			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Influenza like illness			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hypersensitivity			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sinus congestion			



subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Depressed mood			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Depression			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Investigations			
Albumin urine present			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Blood iron decreased			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Intraocular pressure increased			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Lymphocyte count decreased			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Injury, poisoning and procedural complications			
Chest injury			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Corneal abrasion			
subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Fall			
subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Procedural nausea			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Stress fracture			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Wrist fracture			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Hyposmia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
IIIrd nerve paralysis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
IVth nerve paralysis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
VIIth nerve paralysis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Blepharospasm			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Cataract			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Conjunctival haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Corneal erosion			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye pain			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eye pruritis			

subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Eyelid oedema			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Lenticular opacities			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Posterior capsule opacification			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Retinal haemorrhage			
subjects affected / exposed	2 / 4 (50.00%)		
occurrences (all)	2		
Vision blurred			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vitreous haematoma			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vitreous detachment			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Vitreous haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Colitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Diarrhoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Tongue ulceration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Hepatobiliary disorders Early satiety subjects affected / exposed occurrences (all)  Hepatic cirrhosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0  0 / 4 (0.00%) 0		
Skin and subcutaneous tissue disorders Blister subjects affected / exposed occurrences (all)  Dermatitis contact subjects affected / exposed occurrences (all)  Rash subjects affected / exposed occurrences (all)  Skin lesion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0  0 / 4 (0.00%) 0  0 / 4 (0.00%) 0  0 / 4 (0.00%) 0		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)  Back pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0  1 / 4 (25.00%) 1		

Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Myalgia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Neck pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Pain in extremity subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Rheumatoid arthritis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Infections and infestations			
Cellulitis subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Ear infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Gastroenteritis viral subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1		
Influenza subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Localised infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Lower respiratory tract infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
Nasopharyngitis			

subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Respiratory tract infection viral			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Tonsillitis			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Viral infection			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		
Gout			
subjects affected / exposed	0 / 4 (0.00%)		
occurrences (all)	0		

Hyperkalaemia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0		
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## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26875003>