



## Clinical trial results:

**A Multicentre Phase III Double-masked Randomised Controlled Non-Inferiority Trial comparing the clinical and cost effectiveness of intravitreal therapy with ranibizumab (Lucentis) vs aflibercept (Eylea) vs bevacizumab (Avastin) for Macular Oedema due to Central Retinal Vein Occlusion (CRVO).**

### Summary

EudraCT number	2014-000272-26
Trial protocol	GB
Global end of trial date	21 November 2018

### Results information

Result version number	v1 (current)
This version publication date	25 April 2020
First version publication date	25 April 2020
Summary attachment (see zip file)	End of study summary report (LEAVO.END.OF.STUDY.REPORT.pdf)

### Trial information

#### Trial identification

Sponsor protocol code	HYKP1021
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#### Additional study identifiers

ISRCTN number	ISRCTN13623634
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Moorfields Eye Hospital NHS Foundation Trust
Sponsor organisation address	162 City Road, London, United Kingdom, EC1V 2PD
Public contact	Tania West, Moorfields Eye Hospital NHS Foundation Trust, 44 020 7253 3411 x2937 ,
Scientific contact	Tania West, Moorfields Eye Hospital NHS Foundation Trust, 44 02072533411, moorfields.resadmin@nhs.net

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	21 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2018
Global end of trial reached?	Yes
Global end of trial date	21 November 2018
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

To determine if bevacizumab or aflibercept are as effective as ranibizumab in reducing visual loss from MO due to CRVO, whether they have an equivalent side effect profile and whether either could be considered as a recommended NHS treatment based on non-inferior clinical effectiveness and superior cost-effectiveness to ranibizumab.

Protection of trial subjects:

Patients were fully consented following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. They were advised that any data collected were held and used in accordance with the Data Protection Act 1998. Patients were given at least 24 hours after receiving the PIS to consider taking part. Data was anonymized and stored securely.

Complications such as the development of ischaemic CRVO, NVA, NVI, NVG, NVE and NVD in the study eye were recorded as adverse events. Diagnosis and management of these complications of CRVO in the study was based on investigator discretion and local practice.

The MHRA definitions of adverse and serious adverse events were adopted for this trial. Adverse events were reported by the site in the adverse events log in the eCRF. All SAEs, SARs & SUSARs were recorded and reported on the serious adverse event form to the Chief Investigator / delegate within 24 hours of learning of their occurrence.

The trial had a designated Trial Steering Committee which was responsible for monitoring the overall integrity, conduct and safety of the trial and an independent Data Monitoring and Ethics Committee to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.

The study would have been discontinued on the basis of new safety information, or for other reasons given by the DMEC and/or TSC, Sponsor, regulatory authority or Research Ethics Committee concerned.

All members of the research team were compliant with Good Clinical Practice guidelines.

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Background therapy:

Retinal laser therapy was used for complications such as ischaemic CRVO, NVA, NVI, NVG, NVE and NVD.

Evidence for comparator:

First line therapy of macular oedema is repeated intravitreal injections of anti-VEGF agents to block the action of VEGF thus reducing capillary permeability.

Ranibizumab was licensed by the FDA and EMA for MO due to CRVO in 2012 based on the CRUISE study data that showed monthly intraocular ranibizumab therapy improved mean BCVA by +15 ETDRS letters at 6 months and a PRN regimen with monthly monitoring improved mean BCVA by +14 letters at 12 months.

Aflibercept was FDA and EMA licensed for CRVO in 2014 based on the GALILEO and COPERNICUS studies that showed a mean gain of +16.2 letters BVCA at 12 and +13.0 at 24 months. Despite these results and that it was non-inferior to ranibizumab when given 8 weekly after a loading phase in nvAMD suggesting improved cost effectiveness, no clinical trial had been undertaken to directly compare it with ranibizumab or bevacizumab even though NICE recommended it for MO due to CRVO (NICE TA305).

Bevacizumab is EMA licensed for the treatment of cancer but is used off-label in the eye. It is substantially cheaper than ranibizumab or aflibercept and has been used in private practice and NHS trusts across the UK for nvAMD, DMO and RVO and other less common indications such as choroidal

neovascularisation due to myopia and retinal dystrophies. It was found to be non-inferior to ranibizumab in the IVAN and CATT studies.

There have been concerns about the possible systemic side effects following intraocular injection of bevacizumab. The NICE TAG 283: Lucentis (ranibizumab) and the TAG 305: Eylea (aflibercept) for MO secondary to CRVO recommended that further head to head trials including bevacizumab were needed for RVO that carefully examined clinical and cost effectiveness. It was therefore proposed to conduct the LEAVO trial in MO due to CRVO to compare the clinical and cost effectiveness of ranibizumab, aflibercept and bevacizumab, and describe the safety profile of each with ocular and systemic adverse events over 24 months.

Actual start date of recruitment	03 December 2014
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: 463
Worldwide total number of subjects	463
EEA total number of subjects	463

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)	138
From 65 to 84 years	284
85 years and over	41

## Subject disposition

### Recruitment

#### Recruitment details:

Recruitment commenced from 1st December 2014 and the last patient was randomised 16th December 2016. 586 patients were assessed across 44 UK NHS Hospitals, of which 463 eligible patients were randomly assigned to receive ranibizumab (n=155), aflibercept (n=154) or bevacizumab (n=154).

### Pre-assignment

#### Screening details:

Demographic data, medical history and ophthalmic history were obtained at screening. Refracted ETDRS visual acuity, undilated examinations for NVI, IOP and RAPD along with dilated fundus examination, SD-OCT, colour fundus photography and fluorescein angiogram were performed. Health economic questionnaires were administered.

### Pre-assignment period milestones

Number of subjects started	463
Number of subjects completed	463

### Period 1

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

#### Blinding implementation details:

Only the pharmacy at the local trial site, the emergency unmasking service and unmasked trial management staff were informed of the treatment arm. The study drug was transferred in a sealed opaque masking bag to the dedicated injection room. The unmasked injector opened the bag and placed the medication out of sight of the patient before they entered the room. There was no record of the subjects' treatment arm in the source notes or case report form

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Ranibizumab arm
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravitreal use

#### Dosage and administration details:

Dosage and route - 0.5mg/50ul intravitreal injection.

After mandated administration at baseline, 4, 8, and 12 weeks, further PRN intervention was administered at weeks 16 and 20 if retreatment criteria were met and VA  $\leq$  83 letters. Whether a treatment was given or not, the patient was reviewed in 4 weeks. From week 24 to week 96, intervals were initially 4 weekly (with a -14 to + 14 day visit window) with the potential to increase to 8 weekly (with a -14 to + 14 day visit window) if criteria for 'Stability' were achieved. Treatment was not given if success criteria (from week 16 onwards) or non-responder treatment suspension criteria (from week 24 onwards) were met. Treatment could be restarted at a later visit if defined criteria were met. Deferral of treatment was allowed under certain circumstances.

<b>Arm title</b>	Aflibercept arm
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	Eylea
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

**Dosage and administration details:**

Dosage and route - 2.0mg/50ul intravitreal injection.

After mandated administration at baseline, 4, 8, and 12 weeks, further PRN intervention was administered at weeks 16 and 20 if retreatment criteria were met and VA  $\leq$  83 letters. Whether a treatment was given or not, the patient was reviewed in 4 weeks. From week 24 to week 96, intervals were initially 4 weekly (with a -14 to + 14 day visit window) with the potential to increase to 8 weekly (with a -14 to + 14 day visit window) if criteria for 'Stability' were achieved. Treatment was not given if success criteria (from week 16 onwards) or non-responder treatment suspension criteria ( from week 24 onwards) were met. Treatment could be restarted at a later visit if defined criteria were met. Deferral of treatment was allowed under certain circumstances.

<b>Arm title</b>	Bevacizumab arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Bevacizumab arm
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

**Dosage and administration details:**

Dosage and route - 1.25mg/50ul intravitreal injection.

After mandated administration at baseline, 4, 8, and 12 weeks, further PRN intervention was administered at weeks 16 and 20 if retreatment criteria were met and VA  $\leq$  83 letters. Whether a treatment was given or not, the patient was reviewed in 4 weeks. From week 24 to week 96, intervals were initially 4 weekly (with a -14 to + 14 day visit window) with the potential to increase to 8 weekly (with a -14 to + 14 day visit window) if criteria for 'Stability' were achieved. Treatment was not given if success criteria (from week 16 onwards) or non-responder treatment suspension criteria ( from week 24 onwards) were met. Treatment could be restarted at a later visit if defined criteria were met. Deferral of treatment was allowed under certain circumstances.

<b>Number of subjects in period 1</b>	Ranibizumab arm	Aflibercept arm	Bevacizumab arm
Started	155	154	154
Completed	135	133	139
Not completed	20	21	15
Adverse event, serious fatal	3	6	4
Moved away	-	2	1
Consent withdrawn by subject	8	6	5
Adverse event, non-fatal	2	1	2
Health deterioration	2	-	-
Lost to follow-up	3	3	1
Deterioration of health	-	2	1
not specified	2	1	1



## Baseline characteristics

### Reporting groups

Reporting group title	Ranibizumab arm
Reporting group description: -	
Reporting group title	Aflibercept arm
Reporting group description: -	
Reporting group title	Bevacizumab arm
Reporting group description: -	

Reporting group values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm
Number of subjects	155	154	154
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	69.2	68.7	69.3
standard deviation	± 13.0	± 13.2	± 12.8
Gender categorical Units: Subjects			
Female	70	60	68
Male	85	94	86
BCVA letter score in the study eye Units: Subjects			
19-38	31	27	27
39-58	56	55	55
59-78	68	72	72
Lens Status, (study eye) Units: Subjects			
Cataract	41	44	46
Pseudophakia	29	20	19
Normal lens	85	90	89
Duration of study eye CRVO Units: Subjects			
<3 months	134	129	138
3-6 months	11	19	8
>6 months	10	6	8
Previous treatment study eye			

Units: Subjects			
Nil	148	149	149
anti-VEGF therapy	6	5	5
not recorded	1	0	0
CRVO ischaemic status at baseline			
Units: Subjects			
Non-ischaemic	137	135	134
Ischaemic	17	19	20
not recorded	1	0	0
Mean BCVA letter score in the study eye			
For one participant in each arm the baseline best refracted visual acuity test was incomplete /test was not performed.			
Units: ETDRS letters			
arithmetic mean	53.6	54.1	54.4
standard deviation	± 15.1	± 15.3	± 14.2
OCT (study eye)			
Central subfield thickness			
Units: µm			
arithmetic mean	731.3	673.2	676.1
standard deviation	± 227.6	± 189.4	± 207.0
Median duration of CRVO			
Units: months			
median	0.9	0.9	0.9
inter-quartile range (Q1-Q3)	0.5 to 1.8	0.4 to 1.7	0.4 to 1.7
OCT Study eye - Total volume			
For Total Volume, data was missing for two ranibizumab patients and one bevacizumab patient.			
Units: mm3			
arithmetic mean	13	12.3	12.8
standard deviation	± 2.9	± 2.6	± 2.9
Systolic blood pressure			
Not recorded for one ranibizumab patient randomized in error			
Units: mmHg			
arithmetic mean	143.1	142.6	143.1
standard deviation	± 17.6	± 17.0	± 15.7
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	80.1	79.1	79.9
standard deviation	± 10.2	± 10.6	± 10.6
<b>Reporting group values</b>	Total		
Number of subjects	463		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		



From 65-84 years	0		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	-		
Gender categorical Units: Subjects			
Female	198		
Male	265		
BCVA letter score in the study eye Units: Subjects			
19-38	85		
39-58	166		
59-78	212		
Lens Status, (study eye) Units: Subjects			
Cataract	131		
Pseudophakia	68		
Normal lens	264		
Duration of study eye CRVO Units: Subjects			
<3 months	401		
3-6 months	38		
>6 months	24		
Previous treatment study eye Units: Subjects			
Nil	446		
anti-VEGF therapy	16		
not recorded	1		
CRVO ischaemic status at baseline Units: Subjects			
Non-ischaemic	406		
Ischaemic	56		
not recorded	1		
Mean BCVA letter score in the study eye			
For one participant in each arm the baseline best refracted visual acuity test was incomplete /test was not performed.			
Units: ETDRS letters arithmetic mean standard deviation	-		
OCT (study eye)			
Central subfield thickness			
Units: µm arithmetic mean standard deviation	-		
Median duration of CRVO Units: months median inter-quartile range (Q1-Q3)	-		

OCT Study eye - Total volume			
For Total Volume, data was missing for two ranibizumab patients and one bevacizumab patient.			
Units: mm3 arithmetic mean standard deviation	-		
Systolic blood pressure			
Not recorded for one ranibizumab patient randomized in error			
Units: mmHg arithmetic mean standard deviation	-		
Diastolic blood pressure Units: mmHg arithmetic mean standard deviation	-		

## End points

### End points reporting groups

Reporting group title	Ranibizumab arm
Reporting group description: -	
Reporting group title	Aflibercept arm
Reporting group description: -	
Reporting group title	Bevacizumab arm
Reporting group description: -	

### Primary: Mean gain in BCVA letter score at 100 weeks - intention to treat

End point title	Mean gain in BCVA letter score at 100 weeks - intention to treat
End point description:	
End point type	Primary
End point timeframe:	100 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	139	
Units: ETDRS Letters				
arithmetic mean (standard deviation)	12.5 ( $\pm$ 21.1)	15.1 ( $\pm$ 18.7)	9.8 ( $\pm$ 21.4)	

### Statistical analyses

Statistical analysis title	Aflibercept vs Ranibizumab (Intention to Treat)
Statistical analysis description:	
The 95% CI for the adjusted mean difference in BCVA letter score between arms at 100 weeks was calculated.	
Intention to treat strategy	
Outcome data was valid and included if the BCVA measure was refracted. All randomised subjects who provided at least one post-baseline valid measurement were included	
Comparison groups	Ranibizumab arm v Aflibercept arm
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
P-value	= 0.0006 <sup>[2]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	2.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.17
upper limit	6.63

Notes:

[1] - Non-inferiority was only concluded if this was declared by both the ITT analysis and the PP analysis at 100 weeks. Non-inferiority was declared if the estimated 95% confidence interval for the difference in means lies wholly above the margin of -5 letters in both ITT and PP analysis models primarily at 100 weeks and secondarily at 52 weeks.

The linear mixed-effects model incorporates 301 participants (n=148 ranibizumab and n=153 aflibercept) with best corrected visual acuity at 100 weeks.

[2] - p-value for non-inferiority -  $p < 0.025$  is significant

<b>Statistical analysis title</b>	Bevacizumab vs Ranibizumab - Intention to treat
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Statistical analysis description:

The 95% CI for the adjusted mean difference in BCVA letter score between arms at 100 weeks was calculated.

Intention to treat strategy

Outcome data was valid and included if the BCVA measure was refracted. All randomised subjects who provided at least one post-baseline valid measurement were included

Comparison groups	Ranibizumab arm v Bevacizumab arm
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[3]</sup>
P-value	= 0.071 <sup>[4]</sup>
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.12
upper limit	2.67

Notes:

[3] - Non-inferiority was only concluded if this was declared by both the ITT analysis and the PP analysis at 100 weeks. Non-inferiority was declared if the estimated 95% confidence interval for the difference in means lies wholly above the margin of -5 letters in both ITT and PP analysis models primarily at 100 weeks and secondarily at 52 weeks.

The linear mixed-effects model incorporates 301 participants (n=148 ranibizumab, n=153 bevacizumab) with best corrected visual acuity at 100 weeks.

[4] - p-value for non-inferiority -  $p < 0.025$  is significant

### Primary: Mean BCVA -100 weeks (per protocol)

End point title	Mean BCVA -100 weeks (per protocol)
End point description:	
End point type	Primary
End point timeframe:	
100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	128	139	
Units: Letter score				
arithmetic mean (standard error)	65.7 (± 1.7)	69.5 (± 1.5)	64.6 (± 1.8)	

## Statistical analyses

Statistical analysis title	Aflibercept versus Ranibizumab (per protocol)
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Statistical analysis description:

The 95% CI for the adjusted mean difference in BCVA letter score between arms at 100 weeks was calculated.

Per protocol strategy

The per protocol (PP) population was defined as a subset of the ITT population who were eligible and received minimal sufficient treatment exposure defined as four treatments correctly assessed and received during the first six visits. For the analysis of the primary outcome, the mixed effects model was re-fitted within the PP population.

Comparison groups	Ranibizumab arm v Aflibercept arm
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[5]</sup>
P-value	< 0.0001 <sup>[6]</sup>
Method	Mixed models analysis
Parameter estimate	adjusted difference
Point estimate	3.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.91
upper limit	7.88

Notes:

[5] - Non-inferiority was only concluded if this was declared by both the ITT analysis and the PP analysis at 100 weeks. Non-inferiority was declared if the estimated 95% confidence interval for the difference in means lies wholly above the margin of -5 letters in both ITT and PP analysis models primarily at 100 weeks and secondarily at 52 weeks.

The linear mixed-effects model incorporates 291 participants (n=145 ranibizumab, n=146 aflibercept) with best corrected visual acuity at 100 weeks.

[6] - p-value for non-inferiority - p<0.025 is significant

Statistical analysis title	Bevacizumab vs Ranibizumab (per protocol)
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Statistical analysis description:

The 95% CI for the adjusted mean difference in BCVA letter score between arms at 100 weeks was calculated.

Per protocol strategy

The per protocol (PP) population was defined as a subset of the ITT population who were eligible and

received minimal sufficient treatment exposure defined as four treatments correctly assessed and received during the first six visits. For the analysis of the primary outcome, the mixed effects model was re-fitted within the PP population.

Comparison groups	Ranibizumab arm v Bevacizumab arm
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[7]</sup>
P-value	= 0.066 <sup>[8]</sup>
Method	Mixed models analysis
Parameter estimate	adjusted difference
Point estimate	-1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.02
upper limit	2.68

Notes:

[7] - Non-inferiority was only concluded if this was declared by both the ITT analysis and the PP analysis at 100 weeks. Non-inferiority was declared if the estimated 95% confidence interval for the difference in means lies wholly above the margin of -5 letters in both ITT and PP analysis models primarily at 100 weeks and secondarily at 52 weeks.

The linear mixed-effects model incorporates 297 participants (n=145 ranibizumab, n=152 bevacizumab) with best corrected visual acuity at 100 weeks.

[8] - p-value for non-inferiority -  $p < 0.025$  is significant

### Secondary: Mean best corrected visual acuity at 52 weeks - Intention to treat

End point title	Mean best corrected visual acuity at 52 weeks - Intention to treat
End point description:	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	139	135	
Units: ETDRS letters				
arithmetic mean (standard error)	65.4 (± 1.6)	67.2 (± 1.5)	66.4 (± 1.6)	

### Statistical analyses

Statistical analysis title	Ranibizumab vs Aflibercept
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Statistical analysis description:

The 95% CI for the adjusted mean difference in BCVA letter score between arms at 52 weeks was calculated.

#### Intention to treat strategy

Outcome data was valid and included if the BCVA measure was refracted. All randomised subjects who provided at least one post-baseline valid measurement were included

Comparison groups	Ranibizumab arm v Aflibercept arm
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[9]</sup>
P-value	= 1.33 <sup>[10]</sup>
Method	Mixed models analysis
Parameter estimate	Adjusted difference
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.62
upper limit	5.28

Notes:

[9] - Non-inferiority was only concluded if this was declared by both the ITT analysis and the PP analysis at 100 weeks. Non-inferiority was declared if the estimated 95% confidence interval for the difference in means lies wholly above the margin of -5 letters in both ITT and PP analysis models primarily at 100 weeks and secondarily at 52 weeks.

The linear mixed-effects model incorporates 301 participants (n=148 ranibizumab, n=153 aflibercept) with best corrected visual acuity at 52 weeks.

[10] - p-value for non-inferiority -  $p < 0.025$  is significant

<b>Statistical analysis title</b>	Ranibizumab vs bevacizumab
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Statistical analysis description:

The 95% CI for the adjusted mean difference in BCVA letter score between arms at 52 weeks was calculated.

#### Intention to treat strategy

Outcome data was valid and included if the BCVA measure was refracted. All randomised subjects who provided at least one post-baseline valid measurement were included

Comparison groups	Ranibizumab arm v Bevacizumab arm
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[11]</sup>
P-value	= 0.0067 <sup>[12]</sup>
Method	Mixed models analysis
Parameter estimate	Adjusted difference
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.97
upper limit	3.94

Notes:

[11] - Non-inferiority was only concluded if this was declared by both the ITT analysis and the PP analysis at 100 weeks. Non-inferiority was declared if the estimated 95% confidence interval for the difference in means lies wholly above the margin of -5 letters in both ITT and PP analysis models primarily at 100 weeks and secondarily at 52 weeks.

The linear mixed-effects model incorporates 301 participants (n=148 ranibizumab, n=153 bevacizumab) with best corrected visual acuity at 52 weeks

[12] - p-value for non-inferiority -  $p < 0.025$  is significant

**Secondary: Mean best corrected visual acuity at 52 weeks - per protocol**

End point title	Mean best corrected visual acuity at 52 weeks - per protocol
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End point description:

End point type	Secondary
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End point timeframe:

52 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	137	133	135	
Units: ETDRS letters				
arithmetic mean (standard error)	65.5 (± 1.7)	68.4 (± 1.4)	66.4 (± 1.35)	

**Statistical analyses**

<b>Statistical analysis title</b>	Aflibercept versus Ranibizumab
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Statistical analysis description:

The 95% CI for the adjusted mean difference in BCVA letter score between arms at 52 weeks was calculated.

Per protocol strategy

The per protocol (PP) population was defined as a subset of the ITT population who were eligible and received minimal sufficient treatment exposure defined as four treatments correctly assessed and received during the first six visits. For the analysis of the primary outcome, the mixed effects model was re-fitted within the PP population.

Comparison groups	Aflibercept arm v Ranibizumab arm
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002 <sup>[13]</sup>
Method	Mixed models analysis
Parameter estimate	adjusted difference
Point estimate	2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.81
upper limit	6.1

Notes:

[13] - p-value for non-inferiority - p<0.025 is significant

<b>Statistical analysis title</b>	Bevacizumab versus Ranibizumab
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Statistical analysis description:

The 95% CI for the adjusted mean difference in BCVA letter score between arms at 52 weeks was calculated.



#### Per protocol strategy

The per protocol (PP) population was defined as a subset of the ITT population who were eligible and received minimal sufficient treatment exposure defined as four treatments correctly assessed and received during the first six visits. For the analysis of the primary outcome, the mixed effects model was re-fitted within the PP population.

Comparison groups	Ranibizumab arm v Bevacizumab arm
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0058 <sup>[14]</sup>
Method	Mixed models analysis
Parameter estimate	adjusted difference
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.88
upper limit	3.98

Notes:

[14] - p-value for non-inferiority -  $p < 0.025$  is significant

#### Secondary: Patients with $\geq 10$ ETDRS letter improvement at 100 weeks

End point title	Patients with $\geq 10$ ETDRS letter improvement at 100 weeks
End point description:	
End point type	Secondary
End point timeframe:	
100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	132	138	
Units: Percentage	63	68	63	

#### Statistical analyses

No statistical analyses for this end point

#### Secondary: Patients with $\geq 10$ ETDRS letter improvement at 52 weeks

End point title	Patients with $\geq 10$ ETDRS letter improvement at 52 weeks
End point description:	
End point type	Secondary
End point timeframe:	
52 weeks	

<b>End point values</b>	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	138	134	
Units: Percentage	60	62	64	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with <15 ETDRS letter decrease at 100 weeks

End point title	Patients with <15 ETDRS letter decrease at 100 weeks
End point description:	
End point type	Secondary
End point timeframe:	
100 weeks	

<b>End point values</b>	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	132	138	
Units: Percentage	90	93	90	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with <15 ETDRS letter decrease at 52 weeks

End point title	Patients with <15 ETDRS letter decrease at 52 weeks
End point description:	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	138	134	
Units: percentage	90	93	95	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with $\geq 30$ ETDRS letter decrease at 100 weeks

End point title	Patients with $\geq 30$ ETDRS letter decrease at 100 weeks
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End point description:

End point type	Secondary
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End point timeframe:

100 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	132	138	
Units: percentage	5	2	6	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with $\geq 30$ ETDRS letter decrease at 52 weeks

End point title	Patients with $\geq 30$ ETDRS letter decrease at 52 weeks
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End point description:

End point type	Secondary
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End point timeframe:

52 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	138	134	
Units: Percentage	6	1	3	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with $\geq 15$ ETDRS letter improvement at 100 weeks

End point title	Patients with $\geq 15$ ETDRS letter improvement at 100 weeks
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End point description:

End point type	Secondary
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End point timeframe:

100 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	132	138	
Units: percentage	47	52	45	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with $> 73$ ETDRS letter score ( $> 20/40$ Snellen equivalent) at 100 weeks

End point title	Patients with $> 73$ ETDRS letter score ( $> 20/40$ Snellen equivalent) at 100 weeks
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End point description:

End point type	Secondary
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End point timeframe:

100 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	139	
Units: Percentage	47	44	41	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with $\leq 58$ ETDRS letter score (20/80) Snellen equivalent) at 100 weeks

End point title	Patients with $\leq 58$ ETDRS letter score (20/80) Snellen equivalent) at 100 weeks
End point description:	
End point type	Secondary
End point timeframe:	
100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	139	
Units: Percentage	39	26	42	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with $< 19$ ETDRS letter score (20/400 Snellen equivalent) at 100 weeks

End point title	Patients with $< 19$ ETDRS letter score (20/400 Snellen equivalent) at 100 weeks
End point description:	
End point type	Secondary
End point timeframe:	
100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	139	
Units: Percentage	4	2	6	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with >73 ETDRS letter score (>20/40- Snellen equivalent) at 52 weeks.

End point title	Patients with >73 ETDRS letter score (>20/40- Snellen equivalent) at 52 weeks.
End point description:	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	139	135	
Units: Percentage	42	42	39	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with ≤58 ETDRS letter (≤20/80 Snellen equivalent) at 52 weeks

End point title	Patients with ≤58 ETDRS letter (≤20/80 Snellen equivalent) at 52 weeks
End point description:	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	139	135	
Units: Percentage	28	25	24	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patients with <19letters ETDRS letter (20/400 Snellen equivalent) at 52 weeks

End point title	Patients with <19letters ETDRS letter (20/400 Snellen equivalent) at 52 weeks
End point description:	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	139	139	135	
Units: Percentage	5	2	5	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change in OCT central subfield thickness from baseline to 100 weeks

End point title	Mean change in OCT central subfield thickness from baseline to 100 weeks
End point description:	
End point type	Secondary
End point timeframe:	
100 weeks	

<b>End point values</b>	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	139	
Units: microns				
arithmetic mean (confidence interval 95%)	-405 (-450 to -360)	-378 (-412 to -343)	-334 (-374 to -293)	

## Statistical analyses

<b>Statistical analysis title</b>	Adjusted difference in CST at 100 weeks
Statistical analysis description:	
There were no clinically relevant differences across treatment groups for the adjusted difference in CST at 100 weeks	
Comparison groups	Ranibizumab arm v Aflibercept arm
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-29.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-60.9
upper limit	2.3

<b>Statistical analysis title</b>	Adjusted difference in CST at 100 weeks
Statistical analysis description:	
There were no clinically relevant differences across treatment groups for the adjusted difference in CST at 100 weeks	
Comparison groups	Ranibizumab arm v Bevacizumab arm
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	21.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	53.4

## Secondary: Mean OCT macular volume at 100 weeks

<b>End point title</b>	Mean OCT macular volume at 100 weeks
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End point description:	
There was no difference in mean macular volume in each study group at 100 weeks	
End point type	Secondary
End point timeframe:	
100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	135	
Units: cubic millimetre				
arithmetic mean (standard error)	8.9 ( $\pm$ 0.1)	8.6 ( $\pm$ 0.1)	9.1 ( $\pm$ 0.2)	

## Statistical analyses

Statistical analysis title	Adjusted difference between groups at 100 weeks
Statistical analysis description:	
The linear mixed-effects model incorporates 455 participants (n=149 ranibizumab, n=153 aflibercept and n=153 bevacizumab and) with both CST and macular volume at either 52 weeks or 100 weeks.	
Comparison groups	Ranibizumab arm v Aflibercept arm
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.3

Statistical analysis title	Adjusted difference between groups at 100 weeks
Statistical analysis description:	
The linear mixed-effects model incorporates 455 participants (n=149 ranibizumab, n=153 aflibercept and n=153 bevacizumab and) with both CST and macular volume at either 52 weeks or 100 weeks.	
Comparison groups	Ranibizumab arm v Bevacizumab arm
Number of subjects included in analysis	270
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.7

### Secondary: Mean OCT macular volume at 52 weeks

End point title	Mean OCT macular volume at 52 weeks
End point description:	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	140	135	
Units: cubic millimetre				
arithmetic mean (standard error)	9.2 (± 0.2)	9.1 (± 0.2)	9.4 (± 0.2)	

### Statistical analyses

Statistical analysis title	Adjusted difference between groups at 52 weeks
Statistical analysis description:	
The linear mixed-effects model incorporates 455 participants (n=149 ranibizumab, n=153 aflibercept and n=153 bevacizumab and) with both CST and macular volume at either 52 weeks or 100 weeks.	
Comparison groups	Ranibizumab arm v Aflibercept arm
Number of subjects included in analysis	278
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.4

Statistical analysis title	Adjusted difference between groups at 52 weeks
Statistical analysis description:	
The linear mixed-effects model incorporates 455 participants (n=149 ranibizumab, n=153 aflibercept	

and n=153 bevacizumab and) with both CST and macular volume at either 52 weeks or 100 weeks.

Comparison groups	Ranibizumab arm v Bevacizumab arm
Number of subjects included in analysis	273
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.7

### Secondary: Percentage of patients with OCT < 320um at 100 weeks

End point title	Percentage of patients with OCT < 320um at 100 weeks
End point description:	
There was a significantly greater proportion of patients with OCT CST <320µm at 100 weeks for aflibercept (81%) compared to ranibizumab group (66%), 15.3% difference (95% CI 4.9 to 25.7)	
End point type	Secondary
End point timeframe:	
100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	135	
Units: Percentage	66	81	59	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of patients with OCT < 320um at 52 weeks

End point title	Percentage of patients with OCT < 320um at 52 weeks
End point description:	
There was a significantly greater proportion of patients with OCT CST <320µm at 52 weeks for aflibercept (76%), compared to ranibizumab (63%), a 12.4% difference (95% CI 1.7 to 23.1).	
End point type	Secondary
End point timeframe:	
52 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	138	140	135	
Units: percentage	63	76	53	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean number of injections across treatment groups - 100 weeks

End point title	Mean number of injections across treatment groups - 100 weeks
End point description: The difference between aflibercept and ranibizumab groups was meaningful (mean difference week 100 -1.9 (95% CI -2.9 to -0.8))	
End point type	Secondary
End point timeframe: 100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	139	
Units: number				
arithmetic mean (confidence interval 95%)	11.8 (10.9 to 12.7)	10.0 (9.3 to 10.6)	11.5 (10.7 to 12.4)	

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change in retinal non-perfusion at 100 weeks.

End point title	Change in retinal non-perfusion at 100 weeks.
End point description: The novel concentric ring method for analysing non-perfusion in disc areas and developed by the LEAVO group during the study was applicable in 235 of 463 patients randomised who underwent wide angled Optos fluorescein angiography. Of these 187 had images successfully performed at both entry and exit and of these 40 were not graded as they received PRP during the study (n=11), there were poor quality images either at baseline or exit (n=23) or the images were not corrected for peripheral angular distortion (n=6) leaving 147 gradable images. Of these 102 were gradable in more than 85% of the assessed area, were converted into disc areas of non perfusion and form the basis of the comparison.	
End point type	Secondary
End point timeframe: 100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	40	33	30	
Units: disc areas				
median (inter-quartile range (Q1-Q3))	0.0 (-5.6 to 16.6)	6.5 (0.0 to 22.5)	0.0 (-13.2 to 15.2)	

<b>Attachments (see zip file)</b>	Amount of retinal non perfusion per arm and change/non
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Number with no 2 step worsening of non-perfusion on fluorescein angiography

End point title	Number with no 2 step worsening of non-perfusion on fluorescein angiography
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End point description:

Of 463 patients at baseline, 461 underwent FFA. At 100 weeks, 407 completed the ITT analysis of whom 377 underwent FFA, and 30 did not as they declined, had experienced an adverse reaction to the dye at baseline, or there were intravenous cannulation / technical difficulties. Of the 377, 53 could not be graded for other reasons e.g. the patient had received panretinal photocoagulation before or during the study and in 14 all images were ungradable, leaving 310 patients with gradable images (table 13). The percentages of patients in each arm with  $\geq 2$  step worsening in one or more quadrants appeared more frequent in the aflibercept arm compared to bevacizumab but as the number of affected quadrants increased the result across arms tended to converge. Overall the data showed no meaningful difference between treatment groups in terms of the number of patients with at least 2-step worsening of non perfusion in one or more quadrant.

End point type	Secondary
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End point timeframe:

100 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	105	96	109	
Units: Number of patients	73	62	86	

<b>Attachments (see zip file)</b>	Change in capillary non-perfusion (CNP).pdf
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of patients who were persistent non-responders at 100 weeks

End point title	Proportion of patients who were persistent non-responders at 100 weeks
End point description: Persistent non-responders were defined as not more than a 5 letter gain in VA and OCT CST decrease of less than 50 µm at 100 weeks.	
End point type	Secondary
End point timeframe: 100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	135	133	139	
Units: Number	0	0	1	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion with no evidence of macular oedema on OCT - 100 weeks

End point title	Proportion with no evidence of macular oedema on OCT - 100 weeks
End point description:	
End point type	Secondary
End point timeframe: 100 weeks	

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	130	133	
Units: Percentage	41	45	27	

<b>Attachments (see zip file)</b>	OCT anatomical outcomes for macula oedema.pdf
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion with no evidence of sub retinal detachment on OCT - 100 weeks

End point title	Proportion with no evidence of sub retinal detachment on OCT - 100 weeks
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End point description:

End point type	Secondary
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End point timeframe:

100 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	130	133	
Units: percentage	89	85	85	

Attachments (see zip file)	OCT anatomical outcomes for macula oedema.pdf
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### Statistical analyses

No statistical analyses for this end point

### Secondary: Cost effectiveness outcomes

End point title	Cost effectiveness outcomes
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End point description:

The cost-effectiveness analysis found that bevacizumab was the most cost-effective intervention compared with licensed agents (ranibizumab and aflibercept). In the treatment of MO due to CRVO The model-based and within-trial analyses found small differences between the QALYs generated by aflibercept, ranibizumab and bevacizumab, but that bevacizumab led to substantially lower costs. The finding that bevacizumab was the most cost-effective intervention was robust to scenario analyses varying assumptions and data inputs.

End point type	Secondary
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End point timeframe:

100 weeks

End point values	Ranibizumab arm	Aflibercept arm	Bevacizumab arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	154	154	154	
Units: GBP				
arithmetic mean (standard deviation)	11727 ( $\pm$ 2900)	10893 ( $\pm$ 2848)	6227 ( $\pm$ 2700)	

<b>Attachments (see zip file)</b>	Table- cost effectiveness.pdf
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### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

100 weeks

Adverse event reporting additional description:

MHRA definitions of adverse and serious adverse events were adopted. Adverse events were reported in an adverse events log in the eCRF. SAEs, SARs & SUSARs were recorded on an SAE form and reported to the Chief Investigator/delegate within 24 hours of learning of the occurrence.

2 pregnancies reported - 1 patient, 1 spouse - normal neonates.

Assessment type	Systematic
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### Dictionary used

Dictionary name	None
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Dictionary version	0.0
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### Reporting groups

Reporting group title	Ranibizumab arm
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Reporting group description: -

Reporting group title	Aflibercept arm
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Reporting group description: -

Reporting group title	Bevacizumab arm
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Reporting group description: -

<b>Serious adverse events</b>	Ranibizumab arm	Aflibercept arm	Bevacizumab arm
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 155 (18.06%)	41 / 154 (26.62%)	30 / 154 (19.48%)
number of deaths (all causes)	3	6	4
number of deaths resulting from adverse events	2	2	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasias			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	3 / 154 (1.95%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Other events			
subjects affected / exposed	3 / 155 (1.94%)	3 / 154 (1.95%)	3 / 154 (1.95%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Immune system disorders			
Allergies			

subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Respiratory, thoracic and mediastinal disorders			
Respiratory disorders			
subjects affected / exposed	3 / 155 (1.94%)	6 / 154 (3.90%)	9 / 154 (5.84%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiovascular – vascular deaths			
subjects affected / exposed	2 / 155 (1.29%)	2 / 154 (1.30%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	1 / 2	2 / 2	0 / 1
deaths causally related to treatment / all	1 / 2	2 / 2	0 / 1
Cardiovascular – non fatal MI			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular – non fatal stroke			
subjects affected / exposed	2 / 155 (1.29%)	4 / 154 (2.60%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular - other			
subjects affected / exposed	7 / 155 (4.52%)	14 / 154 (9.09%)	8 / 154 (5.19%)
occurrences causally related to treatment / all	0 / 8	1 / 14	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neurological disorders			

subjects affected / exposed	1 / 155 (0.65%)	2 / 154 (1.30%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Hematological disorders			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	0 / 154 (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
Ear and labyrinth disorders			
Ear nose and throat disorders			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
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			
Other ophthalmological disorders			
subjects affected / exposed	2 / 155 (1.29%)	2 / 154 (1.30%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious endophthalmitis			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal tear			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 155 (0.00%)	1 / 154 (0.65%)	2 / 154 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal events			

subjects affected / exposed	7 / 155 (4.52%)	8 / 154 (5.19%)	3 / 154 (1.95%)
occurrences causally related to treatment / all	0 / 8	0 / 8	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Hepatobiliary disorders</b>			
Hepatic disorders			
subjects affected / exposed	1 / 155 (0.65%)	0 / 154 (0.00%)	0 / 154 (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>Skin and subcutaneous tissue disorders</b>			
Dermatological disorders			
subjects affected / exposed	0 / 155 (0.00%)	2 / 154 (1.30%)	0 / 154 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Renal and urinary disorders</b>			
Genitourinary disorders			
subjects affected / exposed	2 / 155 (1.29%)	7 / 154 (4.55%)	4 / 154 (2.60%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Endocrine disorders</b>			
Endocrine disorder			
subjects affected / exposed	0 / 155 (0.00%)	0 / 154 (0.00%)	1 / 154 (0.65%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
<b>Musculoskeletal and connective tissue disorders</b>			
Musculoskeletal disorders			
subjects affected / exposed	1 / 155 (0.65%)	4 / 154 (2.60%)	5 / 154 (3.25%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Ranibizumab arm	Aflibercept arm	Bevacizumab arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 155 (16.13%)	24 / 154 (15.58%)	27 / 154 (17.53%)

Eye disorders			
Conversion to ischaemic CRVO			
subjects affected / exposed	8 / 155 (5.16%)	10 / 154 (6.49%)	7 / 154 (4.55%)
occurrences (all)	8	10	7
Anterior segment neovascularisation			
subjects affected / exposed	5 / 155 (3.23%)	5 / 154 (3.25%)	3 / 154 (1.95%)
occurrences (all)	5	5	3
Retinal Neovascularization			
subjects affected / exposed	1 / 155 (0.65%)	4 / 154 (2.60%)	1 / 154 (0.65%)
occurrences (all)	1	4	1
Vitreous haemorrhage			
subjects affected / exposed	0 / 155 (0.00%)	2 / 154 (1.30%)	4 / 154 (2.60%)
occurrences (all)	0	2	4
IOP elevation			
subjects affected / exposed	13 / 155 (8.39%)	9 / 154 (5.84%)	5 / 154 (3.25%)
occurrences (all)	13	9	5

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 September 2014	Changes to protocol and PIS - to cover MHRA grounds for non-acceptance  Protocol and PIS: Changes to ensure patients use contraception for 6 months after their last intravitreal injection of anti-VEGF therapy Protocol: Changes to exclusion criteria
27 February 2015	Changes to protocol, PIS and ICF.  Protocol: Changes to inclusion and exclusion criteria; treatment allocation guess form; retreatment criteria; criteria for restarting therapy; management of ischemic CRVO, neovascular glaucoma, angle or iris neovascularisation; expectedness; secondary outcome. PIS: To reflect that VA will form part of the routine eye exam; guidance on contraception ICF: To reflect new PIS
16 March 2015	New PI at existing site; removal of site; addition of new site.  PIS: Amended following review of new SPCs; allows sites to use nurse injectors ICF: To reflect new PIS
02 June 2015	Adding new sites
04 August 2015	Adding new sites New PI at existing sites
16 May 2016	Changes to protocol; PIS; ICF  Protocol: Changes to inclusion and exclusion criteria; rescreening; injectors; statistical changes; miscellaneous PIS: Changes to clarify who performs the injections; who prescribes antibiotic drops ICF: To reflect new PIS
11 August 2016	New PI at existing site
20 June 2017	New PI at existing site
22 August 2017	Change of SPC regarding Reference Safety Information
16 July 2018	New PI at existing site
04 September 2018	New PI at existing site

Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study may have enrolled eyes with limited potential for visual improvement (severe CRVO and poor perfusion or good acuity and thus a ceiling effect)

Aflibercept was unlicensed at trial commencement - comparisons with Bevacizumab were post hoc.

Notes:

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## Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31465100>