



Clinical trial results:

A randomised control trial of alternative treatments to Inhibit VEGf in Age-related choroidal Neovascularisation (IVAN)

Summary

EudraCT number	2007-001281-33
Trial protocol	GB
Global end of trial date	31 December 2013

Results information

Result version number	v1 (current)
This version publication date	31 March 2020
First version publication date	31 March 2020

Trial information

Trial identification

Sponsor protocol code	RGHT000449
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Additional study identifiers

ISRCTN number	ISRCTN92166560
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health and Social Care Trust
Sponsor organisation address	Research Office, 2nd Floor King Edward Building, Royal Hospitals, Grosvenor Road, Belfast, United Kingdom, BT12 6BA
Public contact	Research Office, Belfast Health and Social Care Trust, Research.Office@belfasttrust.hscni.net
Scientific contact	Research Office, Belfast Health and Social Care Trust, Research.Office@belfasttrust.hscni.net
Sponsor organisation name	Queen's University Belfast
Sponsor organisation address	Research Governance, Ethics and Integrity, Queen's University Belfast, 63 University Road, Belfast, United Kingdom, BT7 1NN
Public contact	Research Governance, Queen's University Belfast, researchgovernance@qub.ac.uk
Scientific contact	Research Governance, Queen's University Belfast, researchgovernance@qub.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 April 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2012
Global end of trial reached?	Yes
Global end of trial date	31 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate the relative effectiveness of two vascular endothelial growth factor (VEGF) inhibitors, i.e. Lucentis® (ranibizumab) and Avastin® (bevacizumab), delivered into the eye by intravitreal injection on visual outcome in patients with choroidal neovascularisation (CNV) from age-related macular degeneration (AMD). To estimate the effectiveness of more frequent (continuous) versus less frequent (discontinuous) VEGF administration in improving or maintaining visual function, with stringent criteria for restarting treatment to prevent visual acuity loss in patients receiving less frequent treatment.

Protection of trial subjects:

All potential participants were sent or given an invitation letter and patient information leaflet (PIL) (approved by a NHS research ethics committee) describing the study. All participants had time to read the PIL and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wished. Participants had a minimum of 48 hours to decide whether they wished to take part. A member of research staff was available to answer questions that patients may have about the trial. The PIL included a phone number that patients can telephone to obtain more information. All members of the direct healthcare team are contractually bound to abide by standard NHS conditions of confidentiality. All of the clinical staff at the study sites will have attended appropriate courses on GCP and will be familiar with issues concerning informed consent. A member of research staff asked the patient whether he/she has understood the information about the trial, and whether he/she had any more questions before asking the patient if he/she was willing to take part in the trial. Written informed consent was obtained for every trial participant.

Background therapy:

Wet or neovascular macular degeneration is a condition which causes severe sight loss in older people. Until recently, available treatments only slowed down the rate of sight loss with most patients becoming moderately or severely visually impaired despite optimal management. A drug known as Lucentis (Ranibizumab) was found to prevent further sight loss in over 90% of those treated. The treatment involved injection of the drug every 4 weeks into the vitreous jelly of the eye for up to two years. A very similar drug, Avastin (Bevacizumab), but which is much cheaper, also appears to have the same benefits but it had not been tested in randomised controlled trials.

Evidence for comparator:

Intravitreal treatment with ranibizumab, an anti body to vascular endothelial growth factor (VEGF), was shown to be effective in neovascular age related macular degeneration compared with photodynamic therapy or no treatment. Anti-VEGF drugs were thus established as a standard of care for neovascular age-related macular degeneration. Bevacizumab, an antibody to VEGF that is licensed for treatment of bowel cancers, is the parent molecule from which ranibizumab was developed. Small non-randomised studies done while ranibizumab was awaiting marketing authorisation suggested that bevacizumab had similar effectiveness to ranibizumab for treatment of neovascular age-related macular degeneration. These findings were important, because every dose of ranibizumab is expensive and treatment can be needed every month for several years.

There were concerns about possible side effects of both drugs, which had not been directly compared. There is also very little evidence on which to base criteria for stopping treatment and so considerable uncertainty about precisely how much treatment might cost in the longer term; this is a major concern to the NHS, not just because of the drug costs but also because of the costs involved in regular monthly treatment. The absence of robust information about the safety of bevacizumab in the treatment of neovascular age-related macular degeneration and uncertainty about treatment frequency for both

bevacizumab and ranibizumab led us to undertake the Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial in the UK.

The IVAN trial was designed to compare the clinical efficacy of the two drugs and to compare a reduced treatment regimen versus two years of continuous treatment.

Actual start date of recruitment	27 March 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 610
Worldwide total number of subjects	610
EEA total number of subjects	610

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)	27
From 65 to 84 years	447
85 years and over	136

Subject disposition

Recruitment

Recruitment details:

Between 27 March 2008 and 15 October 2010, 2,693 patients were screened for inclusion in the trial and full informed consent was taken from 610 patients who agreed to take part in the study. All potential participants received an information leaflet.

Pre-assignment

Screening details:

Of the 693 patients screened for inclusion in the trial, 28 were identified as ineligible and 37 excluded for other reasons. The remaining 628 patients were randomised into the trial. Five of these 628 participants were randomised in error and a further 13 were not treated, leaving 610 who received the study drugs and were included in the analyses.

Period 1

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

Blinding implementation details:

Allocations were computer generated and concealed with an internet-based system (Sealed Envelope, London, UK). Study participants and clinical assessors (nurses, optometrists, imaging technicians, and clinicians) were masked to drug allocation. Study drugs were dispensed by pharmacy staff who were unmasked, but had no other role in the study. Allocation to continuous or discontinuous treatment was masked up to 3 months, at which point both investigator and participant were unmasked.

Arms

Are arms mutually exclusive?	No
Arm title	Ranibizumab

Arm description:

Intravitreal injections of ranibizumab (0.5mg), either monthly (if randomised to continuous treatment regimen) or as-needed (if randomised to discontinuous treatment regimen).

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

Dosage and administration details:

Administration: Intravitreal injections.

Drug dose: 0.5 mg

Arm title	Bevacizumab
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Arm description:

Intravitreal injections of bevacizumab (1.25mg), either monthly (if randomised to continuous treatment regimen) or as-needed (if randomised to discontinuous treatment regimen).

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

Dosage and administration details:

Administration: Intravitreal injections.

Arm title	Continuous
Arm description: Monthly treatment.	
Arm type	Continuous treatment
No investigational medicinal product assigned in this arm	
Arm title	Discontinuous
Arm description: Treated if pre specified clinical and OCT criteria for active disease were met. If re-treatment was needed, a further cycle of three doses was given monthly.	
Arm type	Discontinuous treatment
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Ranibizumab	Bevacizumab	Continuous
Started	314	296	308
Completed	314	296	308

Number of subjects in period 1	Discontinuous
Started	302
Completed	302

Baseline characteristics

Reporting groups

Reporting group title	Ranibizumab
Reporting group description: Intravitreal injections of ranibizumab (0.5mg), either monthly (if randomised to continuous treatment regimen) or as-needed (if randomised to discontinuous treatment regimen).	
Reporting group title	Bevacizumab
Reporting group description: Intravitreal injections of bevacizumab (1.25mg), either monthly (if randomised to continuous treatment regimen) or as-needed (if randomised to discontinuous treatment regimen).	
Reporting group title	Continuous
Reporting group description: Monthly treatment.	
Reporting group title	Discontinuous
Reporting group description: Treated if pre specified clinical and OCT criteria for active disease were met. If re-treatment was needed, a further cycle of three doses was given monthly.	

Reporting group values	Ranibizumab	Bevacizumab	Continuous
Number of subjects	314	296	308
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			
Age at randomisation			
Units: years			
arithmetic mean	77.8	77.7	77.8
standard deviation	± 7.6	± 7.3	± 8.0
Gender categorical Units: Subjects			
Female	185	181	182
Male	129	115	126
Angina Units: Subjects			
Yes	35	51	45
No	279	245	263
Dyspnoea Units: Subjects			
Yes	57	60	57

No	256	235	249
Missing	1	1	2
Myocardial Infarction			
Units: Subjects			
Yes	24	22	26
No	290	274	282
Transient ischaemic attack			
Units: Subjects			
Yes	20	9	15
No	274	273	276
Missing	20	14	17
Stroke			
Units: Subjects			
Yes	7	7	4
No	307	288	304
Missing	0	1	0
DVT/PE			
DVT/PE = Deep-vein thrombosis or pulmonary embolism.			
Units: Subjects			
Yes	16	18	16
No	297	277	292
Missing	1	1	0
Current or past smoker			
Units: Subjects			
Yes	200	185	194
No	109	110	111
Missing	5	1	3
Foveal centre involvement			
Units: Subjects			
Yes	230	223	235
No	79	66	66
Missing	5	7	7
Choroidal neovascularisation			
Units: Subjects			
Yes	156	162	170
No	149	125	129
Missing	9	9	9
Haemorrhage			
Units: Subjects			
Yes	86	88	89
No	222	204	214
Missing	6	4	5
Other foveal centre involvement			
Units: Subjects			
Yes	47	30	39
No	259	262	262
Missing	8	4	7
No choroidal neovascularisation or unable to grade			
Units: Subjects			
Yes	7	8	4

No	302	286	300
Missing	5	2	4
Geographic atrophy Units: Subjects			
Yes	25	18	24
No	284	277	280
Missing	5	1	4
Blood pressure (Systolic) Units: mmHg			
arithmetic mean	141.9	143.0	143.2
standard deviation	± 19.5	± 19.5	± 19.8
Blood pressure (Diastolic) Units: mmHg			
arithmetic mean	76.4	77.1	77.4
standard deviation	± 10.2	± 9.9	± 10.1
Best corrected visual acuity Units: Letters			
arithmetic mean	61.8	61.1	60.1
standard deviation	± 15.0	± 15.5	± 15.5
Near visual acuity			
Data missing for 7 patients (3 Ranibizumab, 4 Bevacizumab; 5 Continuous, 2 Discontinuous)			
Units: logMAR			
arithmetic mean	0.66	0.67	0.70
standard deviation	± 0.34	± 0.33	± 0.34
Belfast reading index			
Data missing for 34 patients (21 Ranibizumab, 13 Bevacizumab; 21 Continuous, 13 Discontinuous)			
Units: Index			
median	36.9	35.0	33.1
inter-quartile range (Q1-Q3)	15.6 to 65.3	14.0 to 69.6	13.6 to 67.7
Contrast sensitivity			
Data missing for 3 patients (3 Ranibizumab, 0 Bevacizumab; 3 Continuous, 0 Discontinuous)			
Units: Letters			
arithmetic mean	26.2	26.3	26.1
standard deviation	± 6.2	± 5.7	± 6.0
Total thickness at fovea			
Data missing for 53 patients (24 Ranibizumab, 29 Bevacizumab; 27 Continuous, 26 Discontinuous)			
Units: µm			
arithmetic mean	471.6	465.6	473.2
standard deviation	± 192.5	± 183.1	± 187.9
Retinal plus subretinal fluid thickness at fovea			
Data missing for 53 patients (24 Ranibizumab, 29 Bevacizumab; 27 Continuous, 26 Discontinuous)			
Units: µm			
arithmetic mean	271.9	264.0	263.9
standard deviation	± 128.6	± 131.6	± 126.9
Area of lesion, optic disc area			
Data missing for 23 patients (11 Ranibizumab, 12 Bevacizumab; 10 Continuous, 13 Discontinuous)			
Units: µm			
median	3.28	3.97	3.68
inter-quartile range (Q1-Q3)	1.10 to 7.76	1.42 to 8.24	1.27 to 7.81
EQ-5D state score			
Data missing for 2 patients (1 Ranibizumab, 1 Bevacizumab; 0 Continuous, 2 Discontinuous)			

Units: Utility score			
median	0.81	0.85	0.85
inter-quartile range (Q1-Q3)	0.73 to 1.00	0.73 to 1.00	0.73 to 1.00

Reporting group values	Discontinuous	Total	
Number of subjects	302	610	
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			
Age at randomisation			
Units: years			
arithmetic mean	77.6		
standard deviation	± 6.8	-	
Gender categorical			
Units: Subjects			
Female	184	366	
Male	118	244	
Angina			
Units: Subjects			
Yes	41	86	
No	261	524	
Dyspnoea			
Units: Subjects			
Yes	60	117	
No	242	491	
Missing	0	2	
Myocardial Infarction			
Units: Subjects			
Yes	20	46	
No	282	564	
Transient ischaemic attack			
Units: Subjects			
Yes	14	29	
No	271	547	
Missing	17	34	
Stroke			
Units: Subjects			
Yes	10	14	
No	291	595	
Missing	1	1	

DVT/PE			
DVT/PE = Deep-vein thrombosis or pulmonary embolism.			
Units: Subjects			
Yes	18	34	
No	282	574	
Missing	2	2	
Current or past smoker			
Units: Subjects			
Yes	191	385	
No	108	219	
Missing	3	6	
Foveal centre involvement			
Units: Subjects			
Yes	218	453	
No	79	145	
Missing	5	12	
Choroidal neovascularisation			
Units: Subjects			
Yes	148	318	
No	145	274	
Missing	9	18	
Haemorrhage			
Units: Subjects			
Yes	85	174	
No	212	426	
Missing	5	10	
Other foveal centre involvement			
Units: Subjects			
Yes	38	77	
No	259	521	
Missing	5	12	
No choroidal neovascularisation or unable to grade			
Units: Subjects			
Yes	11	15	
No	288	588	
Missing	3	7	
Geographic atrophy			
Units: Subjects			
Yes	19	43	
No	281	561	
Missing	2	6	
Blood pressure (Systolic)			
Units: mmHg			
arithmetic mean	141.7		
standard deviation	± 19.1	-	
Blood pressure (Diastolic)			
Units: mmHg			
arithmetic mean	76.2		
standard deviation	± 10.0	-	
Best corrected visual acuity			

Units: Letters			
arithmetic mean	62.9		
standard deviation	± 15.0	-	
Near visual acuity			
Data missing for 7 patients (3 Ranibizumab, 4 Bevacizumab; 5 Continuous, 2 Discontinuous)			
Units: logMAR			
arithmetic mean	0.63		
standard deviation	± 0.32	-	
Belfast reading index			
Data missing for 34 patients (21 Ranibizumab, 13 Bevacizumab; 21 Continuous, 13 Discontinuous)			
Units: Index			
median	40.0		
inter-quartile range (Q1-Q3)	16.3 to 69.6	-	
Contrast sensitivity			
Data missing for 3 patients (3 Ranibizumab, 0 Bevacizumab; 3 Continuous, 0 Discontinuous)			
Units: Letters			
arithmetic mean	26.4		
standard deviation	± 5.9	-	
Total thickness at fovea			
Data missing for 53 patients (24 Ranibizumab, 29 Bevacizumab; 27 Continuous, 26 Discontinuous)			
Units: µm			
arithmetic mean	464.1		
standard deviation	± 188.2	-	
Retinal plus subretinal fluid thickness at fovea			
Data missing for 53 patients (24 Ranibizumab, 29 Bevacizumab; 27 Continuous, 26 Discontinuous)			
Units: µm			
arithmetic mean	272.4		
standard deviation	± 133.2	-	
Area of lesion, optic disc area			
Data missing for 23 patients (11 Ranibizumab, 12 Bevacizumab; 10 Continuous, 13 Discontinuous)			
Units: µm			
median	3.59		
inter-quartile range (Q1-Q3)	1.16 to 8.42	-	
EQ-5D state score			
Data missing for 2 patients (1 Ranibizumab, 1 Bevacizumab; 0 Continuous, 2 Discontinuous)			
Units: Utility score			
median	0.85		
inter-quartile range (Q1-Q3)	0.73 to 1.00	-	

End points

End points reporting groups

Reporting group title	Ranibizumab
Reporting group description: Intravitreal injections of ranibizumab (0.5mg), either monthly (if randomised to continuous treatment regimen) or as-needed (if randomised to discontinuous treatment regimen).	
Reporting group title	Bevacizumab
Reporting group description: Intravitreal injections of bevacizumab (1.25mg), either monthly (if randomised to continuous treatment regimen) or as-needed (if randomised to discontinuous treatment regimen).	
Reporting group title	Continuous
Reporting group description: Monthly treatment.	
Reporting group title	Discontinuous
Reporting group description: Treated if pre specified clinical and OCT criteria for active disease were met. If re-treatment was needed, a further cycle of three doses was given monthly.	
Subject analysis set title	Ranibizumab: Baseline BCVA in fellow eye ≥ 75
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup: Ranibizumab arm - Baseline BCVA in fellow eye ≥ 75	
Subject analysis set title	Ranibizumab: Baseline BCVA in fellow eye < 75
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup: Ranibizumab arm - Baseline BCVA in fellow eye < 75	
Subject analysis set title	Bevacizumab: Baseline BCVA in fellow eye ≥ 75
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup: Bevacizumab arm - Baseline BCVA in fellow eye ≥ 75	
Subject analysis set title	Bevacizumab: Baseline BCVA in fellow eye < 75
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup: Bevacizumab arm - Baseline BCVA in fellow eye < 75	
Subject analysis set title	Continuous: Baseline BCVA in fellow eye ≥ 75
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup: Continuous arm - Baseline BCVA in fellow eye ≥ 75	
Subject analysis set title	Continuous: Baseline BCVA in fellow eye < 75
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup: Continuous arm - Baseline BCVA in fellow eye < 75	
Subject analysis set title	Discontinuous: Baseline BCVA in fellow eye ≥ 75
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup: Discontinuous arm - Baseline BCVA in fellow eye ≥ 75	
Subject analysis set title	Discontinuous: Baseline BCVA in fellow eye < 75
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subgroup: Discontinuous arm - Baseline BCVA in fellow eye < 75	
Subject analysis set title	Ranibizumab: Baseline BCVA < 55

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Ranibizumab arm - Baseline BCVA in study eye <55	
Subject analysis set title	Ranibizumab: Baseline BCVA ≥55
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Ranibizumab arm - Baseline BCVA in study eye ≥55	
Subject analysis set title	Bevacizumab: Baseline BCVA <55
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Bevacizumab arm - Baseline BCVA in study eye <55	
Subject analysis set title	Bevacizumab: Baseline BCVA ≥55
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Bevacizumab arm - Baseline BCVA in study eye ≥55	
Subject analysis set title	Continuous: Baseline BCVA <55
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Continuous arm - Baseline BCVA in study eye <55	
Subject analysis set title	Continuous: Baseline BCVA ≥55
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Continuous arm - Baseline BCVA in study eye ≥55	
Subject analysis set title	Discontinuous: Baseline BCVA <55
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Discontinuous arm - Baseline BCVA in study eye <55	
Subject analysis set title	Discontinuous: Baseline BCVA ≥55
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Discontinuous arm - Baseline BCVA in study eye ≥55	
Subject analysis set title	Ranibizumab: Baseline CNV size <6mm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Ranibizumab arm - Baseline CNV size <6mm	
Subject analysis set title	Ranibizumab: Baseline CNV size ≥6mm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Ranibizumab arm - Baseline CNV size ≥6mm	
Subject analysis set title	Bevacizumab: Baseline CNV size <6mm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Bevacizumab arm - Baseline CNV size <6mm	
Subject analysis set title	Bevacizumab: Baseline CNV size ≥6mm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Bevacizumab arm - Baseline CNV size ≥6mm	
Subject analysis set title	Continuous arm: Baseline CNV size <6mm
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Continuous arm - Baseline CNV size <6mm	
Subject analysis set title	Continuous arm: Baseline CNV size ≥6mm

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Continuous arm - Baseline CNV size $\geq 6\text{mm}$	
Subject analysis set title	Discontinuous arm: Baseline CNV size $< 6\text{mm}$
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Discontinuous arm - Baseline CNV size $< 6\text{mm}$	
Subject analysis set title	Discontinuous arm: Baseline CNV size $\geq 6\text{mm}$
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Discontinuous arm - Baseline CNV size $\geq 6\text{mm}$	
Subject analysis set title	Ranibizumab: Baseline lesion $< 50\%$ CNV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Ranibizumab arm - Baseline lesion $< 50\%$ CNV	
Subject analysis set title	Ranibizumab: Baseline lesion $\geq 50\%$ CNV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Ranibizumab arm - Baseline lesion $\geq 50\%$ CNV	
Subject analysis set title	Bevacizumab: Baseline lesion $< 50\%$ CNV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Bevacizumab arm - Baseline lesion $< 50\%$ CNV	
Subject analysis set title	Bevacizumab: Baseline lesion $\geq 50\%$ CNV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Bevacizumab arm - Baseline lesion $\geq 50\%$ CNV	
Subject analysis set title	Continuous: Baseline lesion $< 50\%$ CNV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Continuous arm - Baseline lesion $< 50\%$ CNV	
Subject analysis set title	Continuous: Baseline lesion $\geq 50\%$ CNV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Continuous arm - Baseline lesion $\geq 50\%$ CNV	
Subject analysis set title	Discontinuous: Baseline lesion $< 50\%$ CNV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Discontinuous arm - Baseline lesion $< 50\%$ CNV	
Subject analysis set title	Discontinuous: Baseline lesion $\geq 50\%$ CNV
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Discontinuous arm - Baseline lesion $\geq 50\%$ CNV	
Subject analysis set title	Ranibizumab: Baseline RAP absent
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Ranibizumab arm - Baseline RAP absent	
Subject analysis set title	Ranibizumab: Baseline RAP present
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Ranibizumab arm - Baseline RAP present	
Subject analysis set title	Bevacizumab: Baseline RAP absent

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Bevacizumab arm - Baseline RAP absent	
Subject analysis set title	Bevacizumab: Baseline RAP present
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Bevacizumab arm - Baseline RAP present	
Subject analysis set title	Continuous: Baseline RAP absent
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Continuous arm - Baseline RAP absent	
Subject analysis set title	Continuous: Baseline RAP present
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Continuous arm - Baseline RAP present	
Subject analysis set title	Discontinuous: Baseline RAP absent
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Discontinuous arm - Baseline RAP absent	
Subject analysis set title	Discontinuous: Baseline RAP present
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup: Discontinuous arm - Baseline RAP present	
Subject analysis set title	Discontinuous bevacizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis group for resource use and cost effectiveness: Discontinuous bevacizumab	
Subject analysis set title	Continuous bevacizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis group for resource use and cost effectiveness: Continuous bevacizumab	
Subject analysis set title	Discontinuous ranibizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis group for resource use and cost effectiveness: Discontinuous ranibizumab	
Subject analysis set title	Continuous ranibizumab
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Analysis group for resource use and cost effectiveness: Continuous ranibizumab	

Primary: Best corrected visual acuity

End point title	Best corrected visual acuity
End point description:	
Best corrected visual acuity (BCVA) measured as the number of letters read on a standard Early Treatment Diabetic Retinopathy Study chart.	
End point type	Primary
End point timeframe:	
Measured at 0, 3, 6, 9, 12, 15, 18, 21 and 24 months	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Letters				
arithmetic mean (standard deviation)	67.8 (± 17.0)	66.1 (± 18.4)	66.6 (± 17.9)	67.3 (± 17.5)

End point values	Ranibizumab: Baseline BCVA in fellow eye ≥75	Ranibizumab: Baseline BCVA in fellow eye <75	Bevacizumab: Baseline BCVA in fellow eye ≥75	Bevacizumab: Baseline BCVA in fellow eye <75
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	161	145	145	142
Units: Letters				
arithmetic mean (standard deviation)	67.7 (± 18.1)	68.1 (± 15.9)	66.3 (± 17.3)	66.0 (± 19.6)

End point values	Continuous: Baseline BCVA in fellow eye ≥75	Continuous: Baseline BCVA in fellow eye <75	Discontinuous: Baseline BCVA in fellow eye ≥75	Discontinuous: Baseline BCVA in fellow eye <75
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	166	135	140	152
Units: Letters				
arithmetic mean (standard deviation)	67.3 (± 17.6)	66.2 (± 18.1)	66.7 (± 17.8)	67.8 (± 17.5)

End point values	Ranibizumab: Baseline BCVA <55	Ranibizumab: Baseline BCVA ≥55	Bevacizumab: Baseline BCVA <55	Bevacizumab: Baseline BCVA ≥55
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	86	228	96	200
Units: Letters				
arithmetic mean (standard deviation)	53.3 (± 18.0)	72.3 (± 13.8)	49.1 (± 18.3)	73.6 (± 12.6)

End point values	Continuous: Baseline BCVA <55	Continuous: Baseline BCVA ≥55	Discontinuous: Baseline BCVA <55	Discontinuous: Baseline BCVA ≥55
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	104	204	78	224
Units: Letters				
arithmetic mean (standard deviation)	53.0 (± 19.0)	72.8 (± 13.4)	48.3 (± 16.9)	73.0 (± 13.2)

End point values	Ranibizumab: Baseline CNV	Ranibizumab: Baseline CNV	Bevacizumab: Baseline CNV	Bevacizumab: Baseline CNV
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	size <6mm	size ≥6mm	size <6mm	size ≥6mm
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	201	102	181	103
Units: Letters				
arithmetic mean (standard deviation)	68.7 (± 15.9)	65.6 (± 19.0)	67.1 (± 17.6)	64.4 (± 19.6)

End point values	Continuous arm: Baseline CNV size <6mm	Continuous arm: Baseline CNV size ≥6mm	Discontinuous arm: Baseline CNV size <6mm	Discontinuous arm: Baseline CNV size ≥6mm
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	198	100	184	105
Units: Letters				
arithmetic mean (standard deviation)	68.7 (± 16.0)	62.4 (± 20.4)	67.2 (± 17.4)	67.6 (± 17.8)

End point values	Ranibizumab: Baseline lesion <50% CNV	Ranibizumab: Baseline lesion ≥50% CNV	Bevacizumab: Baseline lesion <50% CNV	Bevacizumab: Baseline lesion ≥50% CNV
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	62	224	54	213
Units: Letters				
arithmetic mean (standard deviation)	65.3 (± 18.5)	68.0 (± 16.9)	67.6 (± 17.9)	65.8 (± 18.6)

End point values	Continuous: Baseline lesion <50% CNV	Continuous: Baseline lesion ≥50% CNV	Discontinuous: Baseline lesion <50% CNV	Discontinuous: Baseline lesion ≥50% CNV
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	58	227	58	210
Units: Letters				
arithmetic mean (standard deviation)	64.7 (± 17.7)	66.7 (± 18.1)	67.9 (± 18.6)	67.2 (± 17.5)

End point values	Ranibizumab: Baseline RAP absent	Ranibizumab: Baseline RAP present	Bevacizumab: Baseline RAP absent	Bevacizumab: Baseline RAP present
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	245	43	241	31
Units: Letters				
arithmetic mean (standard deviation)	67.3 (± 17.2)	69.7 (± 16.2)	66.1 (± 18.1)	70.4 (± 17.3)

End point values	Continuous: Baseline RAP absent	Continuous: Baseline RAP present	Discontinuous: Baseline RAP absent	Discontinuous: Baseline RAP present
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Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	248	38	238	36
Units: Letters				
arithmetic mean (standard deviation)	66.2 ($\pm$ 17.8)	70.3 ($\pm$ 16.4)	67.1 ($\pm$ 17.5)	69.5 ($\pm$ 16.9)

Statistical analyses

Statistical analysis title	BCVA by drug
Statistical analysis description:	
Difference in BCVA at 2 years, by drug allocation. Difference is estimated using data from visits 0, 3, 6, 9, 12, 15, 18, 21 and 24, adjusted for center size. Negative values reflect a better mean VA in the ranibizumab group. Non-inferiority limit = -3.5 letters	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.26
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.75
upper limit	1.01

Statistical analysis title	BCVA by treatment regimen
Statistical analysis description:	
Difference in BCVA at 2 years, by treatment regimen. Difference is estimated using data from visits 0, 3, 6, 9, 12, 15, 18, 21 and 24, adjusted for center size. Negative values reflect a better mean VA in the continuous group. Non-inferiority limit = -3.5 letters	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.18
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.01
upper limit	0.75

Statistical analysis title	BCVA by drug: Baseline BCVA in fellow eye ≥ 75
Comparison groups	Ranibizumab: Baseline BCVA in fellow eye ≥ 75 v Bevacizumab: Baseline BCVA in fellow eye ≥ 75
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3 ^[1]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.11
upper limit	1.57

Notes:

[1] - p-value for interaction between baseline BCVA in fellow eye and drug = 0.78

Statistical analysis title	BCVA by drug: Baseline BCVA in fellow eye < 75
Comparison groups	Ranibizumab: Baseline BCVA in fellow eye < 75 v Bevacizumab: Baseline BCVA in fellow eye < 75
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8 ^[2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.91
upper limit	3.01

Notes:

[2] - p-value for interaction between baseline BCVA in fellow eye and drug = 0.78

Statistical analysis title	BCVA by regimen: Baseline BCVA in fellow eye ≥ 75
Comparison groups	Continuous: Baseline BCVA in fellow eye ≥ 75 v Discontinuous: Baseline BCVA in fellow eye ≥ 75
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.47 ^[3]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.59
upper limit	2.11

Notes:

[3] - p-value for interaction between baseline BCVA in fellow eye and treatment regimen = 0.93

Statistical analysis title	BCVA by regimen: Baseline BCVA in fellow eye <75
Comparison groups	Continuous: Baseline BCVA in fellow eye <75 v Discontinuous: Baseline BCVA in fellow eye <75
Number of subjects included in analysis	287
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.29 ^[4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.35
upper limit	1.59

Notes:

[4] - p-value for interaction between baseline BCVA in fellow eye and treatment regimen = 0.93

Statistical analysis title	BCVA by drug: Baseline BCVA <55
Comparison groups	Ranibizumab: Baseline BCVA <55 v Bevacizumab: Baseline BCVA <55
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.022 ^[5]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.64
upper limit	-0.75

Notes:

[5] - p-value for interaction between baseline BCVA and drug = 0.47

Statistical analysis title	BCVA by drug: Baseline BCVA ≥55
Comparison groups	Ranibizumab: Baseline BCVA ≥55 v Bevacizumab: Baseline BCVA ≥55
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.8 ^[6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.44
upper limit	3.16

Notes:

[6] - p-value for interaction between baseline BCVA and drug = 0.47

Statistical analysis title	BCVA by regimen: Baseline BCVA <55
Comparison groups	Continuous: Baseline BCVA <55 v Discontinuous: Baseline BCVA <55
Number of subjects included in analysis	182
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.15 ^[7]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.74
upper limit	1.19

Notes:

[7] - p-value for interaction between baseline BCVA and treatment regimen = 0.89

Statistical analysis title	BCVA by regimen: Baseline BCVA ≥55
Comparison groups	Continuous: Baseline BCVA ≥55 v Discontinuous: Baseline BCVA ≥55
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.53 ^[8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	1.9

Notes:

[8] - p-value for interaction between baseline BCVA and treatment regimen = 0.89

Statistical analysis title	BCVA by drug: Baseline CNV size <6mm
Comparison groups	Bevacizumab: Baseline CNV size <6mm v Ranibizumab: Baseline CNV size <6mm

Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.13 ^[9]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.15
upper limit	0.66

Notes:

[9] - p-value for interaction between baseline CNV size and drug = 0.33

Statistical analysis title	BCVA by drug: Baseline CNV size ≥ 6 mm
Comparison groups	Ranibizumab: Baseline CNV size ≥ 6 mm v Bevacizumab: Baseline CNV size ≥ 6 mm
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.69 ^[10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.18
upper limit	4.81

Notes:

[10] - p-value for interaction between baseline CNV size and drug = 0.33

Statistical analysis title	BCVA by regimen: Baseline CNV size < 6 mm
Comparison groups	Continuous arm: Baseline CNV size < 6 mm v Discontinuous arm: Baseline CNV size < 6 mm
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.02 ^[11]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.36
upper limit	-0.55

Notes:

[11] - p-value for interaction between baseline CNV size and treatment regimen = 0.26

Statistical analysis title	BCVA by regimen: Baseline CNV size $\geq 6\text{mm}$
Comparison groups	Continuous arm: Baseline CNV size $\geq 6\text{mm}$ v Discontinuous arm: Baseline CNV size $\geq 6\text{mm}$
Number of subjects included in analysis	205
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4 ^[12]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.28
upper limit	5.72

Notes:

[12] - p-value for interaction between baseline CNV size and treatment regimen = 0.26

Statistical analysis title	BCVA by drug: Baseline lesion $< 50\%$ CNV
Comparison groups	Ranibizumab: Baseline lesion $< 50\%$ CNV v Bevacizumab: Baseline lesion $< 50\%$ CNV
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.68 ^[13]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.26
upper limit	6.56

Notes:

[13] - p-value for interaction between baseline lesion CNV proportion and drug = 0.36

Statistical analysis title	BCVA by drug: Baseline lesion $\geq 50\%$ CNV
Comparison groups	Bevacizumab: Baseline lesion $\geq 50\%$ CNV v Ranibizumab: Baseline lesion $\geq 50\%$ CNV
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.18 ^[14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.67
upper limit	0.89

Notes:

[14] - p-value for interaction between baseline lesion CNV proportion and drug = 0.36

Statistical analysis title	BCVA by regimen: Baseline lesion <50% CNV
Comparison groups	Continuous: Baseline lesion <50% CNV v Discontinuous: Baseline lesion <50% CNV
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.13 ^[15]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.58
upper limit	1.21

Notes:

[15] - p-value for interaction between baseline lesion CNV proportion and treatment regimen = 0.63

Statistical analysis title	BCVA by regimen: Baseline lesion ≥50% CNV
Comparison groups	Continuous: Baseline lesion ≥50% CNV v Discontinuous: Baseline lesion ≥50% CNV
Number of subjects included in analysis	437
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.49 ^[16]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.76
upper limit	1.81

Notes:

[16] - p-value for interaction between baseline lesion CNV proportion and treatment regimen = 0.63

Statistical analysis title	BCVA by drug: Baseline RAP absent
Comparison groups	Ranibizumab: Baseline RAP absent v Bevacizumab: Baseline RAP absent
Number of subjects included in analysis	486
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.16 ^[17]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.91

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.55
upper limit	0.73

Notes:

[17] - p-value for interaction between baseline RAP present/absent and drug = 0.71

Statistical analysis title	BCVA by drug: Baseline RAP present
Comparison groups	Ranibizumab: Baseline RAP present v Bevacizumab: Baseline RAP present
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.3 ^[18]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.27
upper limit	10.48

Notes:

[18] - p-value for interaction between baseline RAP present/absent and drug = 0.71

Statistical analysis title	BCVA by regimen: Baseline RAP absent
Comparison groups	Continuous: Baseline RAP absent v Discontinuous: Baseline RAP absent
Number of subjects included in analysis	486
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.2 ^[19]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.38
upper limit	0.9

Notes:

[19] - p-value for interaction between baseline RAP present/absent and treatment regimen = 0.85

Statistical analysis title	BCVA by regimen: Baseline RAP present
Comparison groups	Continuous: Baseline RAP present v Discontinuous: Baseline RAP present

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.41 ^[20]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.67
upper limit	3.95

Notes:

[20] - p-value for interaction between baseline RAP present/absent and treatment regimen = 0.85

Statistical analysis title	BCVA by drug: Sensitivity analysis 1
Statistical analysis description:	
Sensitivity analysis of the primary outcome: excluding measurements taken 1 month later, when the main study visit was missed.	
Comparison groups	Bevacizumab v Ranibizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.26
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.73
upper limit	1.03

Statistical analysis title	BCVA by treatment regimen: Sensitivity analysis 1
Statistical analysis description:	
Sensitivity analysis of the primary outcome: excluding measurements taken 1 month later, when the main study visit was missed.	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.19
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.98
upper limit	0.78

Statistical analysis title	BCVA by drug: Sensitivity analysis 2
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Statistical analysis description:

Sensitivity analysis of the primary outcome: including data only for the study visits at which all functional outcomes were assessed (visits 0, 3, 6, 12, 18 and 24).

Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.16
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.08
upper limit	0.68

Statistical analysis title	BCVA by treatment regimen: Sensitivity analysis 2
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Statistical analysis description:

Sensitivity analysis of the primary outcome: including data only for the study visits at which all functional outcomes were assessed (visits 0, 3, 6, 12, 18 and 24).

Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.19
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.97
upper limit	0.79

Secondary: Frequencies of adverse events: Death from any cause

End point title	Frequencies of adverse events: Death from any cause
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End point description:	
Death from any cause	
End point type	Secondary
End point timeframe:	
Duration of trial follow-up (maximum 2 years)	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients				
Yes	15	15	10	20
No	299	281	298	182

Statistical analyses

Statistical analysis title	Death from any cause, by drug
Statistical analysis description:	
ORs < 1 reflect fewer deaths during the 2 years of follow-up in the ranibizumab arm.	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.91
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	2.02

Statistical analysis title	Death from any cause, by treatment regimen
Statistical analysis description:	
ORs < 1 reflect fewer deaths during the 2 years of follow-up in the continuous arm.	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.03

Secondary: Frequencies of adverse events: Arteriothrombotic event or heart failure

End point title	Frequencies of adverse events: Arteriothrombotic event or heart failure
End point description: Arteriothrombotic event (MI, stroke, death from a vascular cause) or heart failure	
End point type	Secondary
End point timeframe: Duration of trial follow-up (maximum 2 years)	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients				
Yes	20	12	12	20
No	294	284	296	282

Statistical analyses

Statistical analysis title	Arteriothrombotic or heart failure, by drug
Statistical analysis description: ORs < 1 reflect fewer events during the 2 years of follow-up in the ranibizumab arm.	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.16
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	3.57

Statistical analysis title	Arteriothrombotic or heart failure, by regimen
Statistical analysis description: ORs < 1 reflect fewer events during the 2 years of follow-up in the continuous arm.	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.13
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.27
upper limit	1.19

Secondary: Frequencies of adverse events: Any vascular event

End point title	Frequencies of adverse events: Any vascular event
End point description: Vascular events include arteriothrombotic events, heart failure, deep-vein thrombosis, pulmonary embolism, transient ischaemic attack, hospitalisation for angina, and non-ocular haemorrhage	
End point type	Secondary
End point timeframe: Duration of trial follow-up (maximum 2 years)	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients				
Yes	31	19	21	29
No	283	277	287	273

Statistical analyses

Statistical analysis title	Any vascular event, by drug
Statistical analysis description: ORs < 1 reflect fewer events during the 2 years of follow-up in the ranibizumab arm.	
Comparison groups	Ranibizumab v Bevacizumab

Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	3.01

Statistical analysis title	Any vascular event, by treatment regimen
Statistical analysis description: ORs < 1 reflect fewer events during the 2 years of follow-up in the continuous arm.	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.21
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.24

Secondary: Frequencies of adverse events: Any vascular event or death	
End point title	Frequencies of adverse events: Any vascular event or death
End point description:	
End point type	Secondary
End point timeframe:	
Duration of trial follow-up (maximum 2 years)	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients				
Yes	38	28	27	39
No	276	268	281	263

Statistical analyses

Statistical analysis title	Any vascular event or death, by drug
Statistical analysis description:	
ORs < 1 reflect fewer events during the 2 years of follow-up in the ranibizumab arm.	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.25
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.29

Statistical analysis title	Any vascular event or death, by treatment regimen
Statistical analysis description:	
ORs < 1 reflect fewer events during the 2 years of follow-up in the continuous arm.	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.09

Secondary: Frequencies of adverse events: Any systemic event

End point title	Frequencies of adverse events: Any systemic event
End point description: ≥1 serious systemic event (includes any non-ocular serious adverse event)	
End point type	Secondary
End point timeframe: Duration of trial follow-up (maximum 2 years)	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients				
Yes	81	80	74	87
No	233	216	234	215

Statistical analyses

Statistical analysis title	Any systemic event, by drug
Statistical analysis description: ORs < 1 reflect fewer events during the 2 years of follow-up in the ranibizumab arm	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.82
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.39

Statistical analysis title	Any systemic event, by treatment regimen
Statistical analysis description: ORs < 1 reflect fewer events during the 2 years of follow-up in the continuous arm	
Comparison groups	Continuous v Discontinuous

Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.16
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.11

Secondary: Health-related quality of life: EQ-5D

End point title	Health-related quality of life: EQ-5D
End point description:	For the EQ-5D utility index, higher summary scores represent better utility.
End point type	Secondary
End point timeframe:	Participants completed the EQ-5D at visits 0, 3, 12 and 24

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Score				
median (inter-quartile range (Q1-Q3))	0.85 (0.73 to 1.00)	0.85 (0.73 to 1.00)	0.85 (0.73 to 1.00)	0.85 (0.73 to 1.00)

Statistical analyses

Statistical analysis title	EQ-5D score, by drug
Statistical analysis description:	For EQ-5D no suitable transformation could be found and so data were dichotomized as 'perfect health' (EQ-5D score of 1) compared with less than perfect health. ORs <1 reflect higher quality of life during the 2 years of follow-up in the ranibizumab arm.
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.25

Statistical analysis title	EQ-5D score, by treatment regimen
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Statistical analysis description:

For EQ-5D no suitable transformation could be found and so data were dichotomized as 'perfect health' (EQ-5D score of 1) compared with less than perfect health. ORs <1 reflect higher quality of life during the 2 years of follow-up in the continuous arm

Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.64
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.29

Secondary: Health-related quality of life: MacDQoI

End point title	Health-related quality of life: MacDQoI
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End point description:

MacDQoI (Macular disease Dependent Quality of Life) is an instrument designed to assess macular disease-specific quality of life. Lower scores represent less impact of nAMD on quality of life.

End point type	Secondary
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End point timeframe:

Administered by telephone after visits 3, 12 and 24.

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Score				
median (inter-quartile range (Q1-Q3))	-1.5 (-2.8 to -0.3)	-1.4 (-2.7 to -0.4)	-1.3 (-2.7 to -0.3)	-1.6 (-3.0 to -0.4)

Statistical analyses

Statistical analysis title	MacDQoL, by drug
Statistical analysis description: For MacDQoL, the outcome was transformed from original scale of -9 to +3 to a scale of -3 to +9, and analysed using a log transformation. The GMR is, therefore, interpreted as the GMR of the MacDQoL score, and not of the MacDQoL score directly. GMR <1 reflect higher quality of life during the 2 years of follow-up in the ranibizumab arm	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.42

Statistical analysis title	MacDQoL, by treatment regimen
Statistical analysis description: For MacDQoL, the outcome was transformed from original scale of -9 to +3 to a scale of -3 to +9, and analysed using a log transformation. The GMR is, therefore, interpreted as the GMR of the MacDQoL score, and not of the MacDQoL score directly. GMR <1 reflect higher quality of life during the 2 years of follow-up in the continuous arm	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.28

Secondary: Treatment satisfaction: MacTSQ

End point title	Treatment satisfaction: MacTSQ
End point description: MacTSQ (Macular disease Treatment Satisfaction Questionnaire) is an instrument designed to assess patients' satisfaction with treatment for nAMD. Higher summary scores represent a higher treatment satisfaction.	
End point type	Secondary

End point timeframe:

Administered by telephone after visits 3, 12 and 24.

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Score				
median (inter-quartile range (Q1-Q3))	66 (61.5 to 70)	65 (60 to 69)	65.5 (61 to 69)	66 (60 to 69)

Statistical analyses

Statistical analysis title	MacTSQ, by drug
Statistical analysis description: For MacTSQ at 2 years, no suitable transformation could be found and so data were dichotomized (MacTSQ < median TSQ score over all time points vs. ≥ median TSQ score over all time points). ORs <1 reflect higher quality of life during the 2 years of follow-up in the ranibizumab arm.	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.16

Statistical analysis title	MacTSQ, by treatment regimen
Statistical analysis description: For MacTSQ at 2 years, no suitable transformation could be found and so data were dichotomized (MacTSQ < median TSQ score over all time points vs. ≥ median TSQ score over all time points). ORs <1 reflect higher quality of life during the 2 years of follow-up in the continuous arm.	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.68

Secondary: Resource use: Injection consultation

End point title	Resource use: Injection consultation
End point description:	
Measured as the number of episodes of injection consultations.	
End point type	Secondary
End point timeframe:	
Resource use used by the average patient during 2-year study period	

End point values	Discontinuous bevacizumab	Continuous bevacizumab	Discontinuous ranibizumab	Continuous ranibizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	150	156	158
Units: Number of consultations				
arithmetic mean (confidence interval 95%)	13.0 (12.3 to 13.8)	22.0 (21.6 to 22.4)	12.7 (12.0 to 13.4)	21.7 (21.2 to 22.1)

Statistical analyses

Statistical analysis title	Injection consultations, by drug
Statistical analysis description:	
Ranibizumab vs. bevacizumab	
Comparison groups	Discontinuous bevacizumab v Continuous bevacizumab v Discontinuous ranibizumab v Continuous ranibizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.4

Statistical analysis title	Injection consultations, by treatment regimen
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Statistical analysis description:

Continuous vs. discontinuous

Comparison groups	Discontinuous bevacizumab v Continuous bevacizumab v Discontinuous ranibizumab v Continuous ranibizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	9
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.3
upper limit	9.7

Secondary: Resource use: Monitoring consultations

End point title	Resource use: Monitoring consultations
End point description:	
Measured as the number of episodes of monitoring consultations.	
End point type	Secondary
End point timeframe:	
Resource use used by the average patient during 2-year study period	

End point values	Discontinuous bevacizumab	Continuous bevacizumab	Discontinuous ranibizumab	Continuous ranibizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	150	156	158
Units: Number of consultations				
arithmetic mean (confidence interval 95%)	13.2 (12.7 to 13.8)	7.1 (6.9 to 7.4)	13.7 (13.1 to 14.2)	7.6 (7.4 to 7.9)

Statistical analyses

Statistical analysis title	Monitoring consultations, by drug
Statistical analysis description:	
Ranibizumab vs. bevacizumab	
Comparison groups	Continuous bevacizumab v Discontinuous ranibizumab v Discontinuous bevacizumab v Continuous ranibizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.9

Statistical analysis title	Monitoring consultations, by treatment regimen
Statistical analysis description:	
Continuous vs. discontinuous	
Comparison groups	Discontinuous bevacizumab v Continuous bevacizumab v Discontinuous ranibizumab v Continuous ranibizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.5
upper limit	-5.6

Secondary: Resource use: Bed-days linked to expected SAEs

End point title	Resource use: Bed-days linked to expected SAEs
End point description:	
Measured as the number of episodes of bed-days linked to expected SAEs.	
End point type	Secondary
End point timeframe:	
Resource use used by the average patient during 2-year study period	

End point values	Discontinuous bevacizumab	Continuous bevacizumab	Discontinuous ranibizumab	Continuous ranibizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	150	156	158
Units: Days				
arithmetic mean (confidence interval 95%)	1.0 (-0.2 to 2.1)	0.8 (0.1 to 1.4)	0.7 (0.2 to 1.2)	0.3 (0.0 to 0.6)

Statistical analyses

Statistical analysis title	Bed-days, by drug (continuous arm)
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Statistical analysis description:

Continuous arm: Ranibizumab vs. bevacizumab

Comparison groups	Continuous bevacizumab v Continuous ranibizumab
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.3

Statistical analysis title

Bed-days, by drug (discontinuous arm)

Statistical analysis description:

Discontinuous arm: Ranibizumab vs. bevacizumab

Comparison groups	Discontinuous bevacizumab v Discontinuous ranibizumab
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1

Statistical analysis title

Bed-days, by treatment regimen (ranibizumab arm)

Statistical analysis description:

Ranibizumab arm: Continuous vs. discontinuous

Comparison groups	Discontinuous ranibizumab v Continuous ranibizumab
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.3

Statistical analysis title	Bed-days, by treatment regimen (bevacizumab)
Statistical analysis description:	
Bevacizumab arm: Continuous vs. discontinuous	
Comparison groups	Discontinuous bevacizumab v Continuous bevacizumab
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	1.1

Secondary: Resource use: Ambulatory consultations

End point title	Resource use: Ambulatory consultations
End point description:	
Measured as the number of episodes of ambulatory resource use, when an 'episode' encompasses all contacts with medical professionals on the same date. For example, seeing a GP and a practice nurse on the same date is counted as one ambulatory consultation in this analysis.	
End point type	Secondary
End point timeframe:	
Resource use used by the average patient during 2-year study period. Consultations within 30 days of expected (S)AEs.	

End point values	Discontinuous bevacizumab	Continuous bevacizumab	Discontinuous ranibizumab	Continuous ranibizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	150	156	158
Units: Number of consultations				
arithmetic mean (confidence interval 95%)	2.8 (2.2 to 3.5)	3.1 (2.4 to 3.7)	2.8 (2.3 to 3.3)	3.1 (2.4 to 3.9)

Statistical analyses

Statistical analysis title	Ambulatory consultations, by drug (continuous)
Statistical analysis description:	
Continuous arm: Ranibizumab vs. bevacizumab	
Comparison groups	Continuous bevacizumab v Continuous ranibizumab

Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	1.1

Statistical analysis title	Ambulatory consultations, by drug (discontinuous)
Statistical analysis description:	
Discontinuous arm: Ranibizumab vs. bevacizumab	
Comparison groups	Discontinuous bevacizumab v Discontinuous ranibizumab
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.8

Statistical analysis title	Ambulatory consultations, by regimen (ranibizumab)
Statistical analysis description:	
Ranibizumab arm: Continuous vs. discontinuous	
Comparison groups	Discontinuous ranibizumab v Continuous ranibizumab
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.2

Statistical analysis title	Ambulatory consultations, by regimen (bevacizumab)
Statistical analysis description:	
Bevacizumab arm: Continuous vs. discontinuous	

Comparison groups	Discontinuous bevacizumab v Continuous bevacizumab
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.1

Secondary: Resource use: Changes in medications

End point title	Resource use: Changes in medications
End point description:	Changes in medications associated with expected (S)AEs.
End point type	Secondary
End point timeframe:	Resource use used by the average patient during 2-year study period.

End point values	Discontinuous bevacizumab	Continuous bevacizumab	Discontinuous ranibizumab	Continuous ranibizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	150	156	158
Units: Number of changes				
arithmetic mean (confidence interval 95%)	3.0 (2.5 to 3.6)	2.6 (2.2 to 3.1)	2.8 (2.2 to 3.4)	3.0 (2.4 to 3.6)

Statistical analyses

Statistical analysis title	Changes in medication, by drug (continuous)
Statistical analysis description:	Continuous arm: Ranibizumab vs. bevacizumab
Comparison groups	Continuous bevacizumab v Continuous ranibizumab
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.1

Statistical analysis title	Changes in medication, by drug (discontinuous)
Statistical analysis description:	
Discontinuous arm: Ranibizumab vs. bevacizumab	
Comparison groups	Discontinuous bevacizumab v Discontinuous ranibizumab
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	0.6

Statistical analysis title	Changes in medication, by regimen (ranibizumab)
Statistical analysis description:	
Ranibizumab arm: Continuous vs. discontinuous	
Comparison groups	Discontinuous ranibizumab v Continuous ranibizumab
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1

Statistical analysis title	Changes in medication, by regimen (bevacizumab)
Statistical analysis description:	
Bevacizumab arm: Continuous vs. discontinuous	
Comparison groups	Continuous bevacizumab v Discontinuous bevacizumab
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	0.3

Secondary: Cost effectiveness: QALYs

End point title	Cost effectiveness: QALYs
End point description:	
End point type	Secondary
End point timeframe:	
Mean QALYs per patient over the 2-year trial period.	

End point values	Discontinuous bevacizumab	Continuous bevacizumab	Discontinuous ranibizumab	Continuous ranibizumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	146	150	156	158
Units: QALY				
arithmetic mean (confidence interval 95%)	1.584 (1.583 to 1.630)	1.604 (1.563 to 1.645)	1.582 (1.530 to 1.634)	1.608 (1.565 to 1.651)

Statistical analyses

Statistical analysis title	QALY, by drug (continuous)
Statistical analysis description:	
Continuous arm: Ranibizumab vs. bevacizumab	
Comparison groups	Continuous bevacizumab v Continuous ranibizumab
Number of subjects included in analysis	308
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.004
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.046
upper limit	0.054

Statistical analysis title	QALY, by drug (discontinuous)
Statistical analysis description:	
Discontinuous arm: Ranibizumab vs. bevacizumab	

Comparison groups	Discontinuous bevacizumab v Discontinuous ranibizumab
Number of subjects included in analysis	302
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-0.002
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.064
upper limit	0.06

Statistical analysis title	QALY, by treatment regimen (ranibizumab)
Statistical analysis description:	
Ranibizumab arm: Continuous vs. discontinuous	
Comparison groups	Discontinuous ranibizumab v Continuous ranibizumab
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.026
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.085

Statistical analysis title	QALY, by treatment regimen (bevacizumab)
Statistical analysis description:	
Bevacizumab arm: Continuous vs. discontinuous	
Comparison groups	Discontinuous bevacizumab v Continuous bevacizumab
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.032
upper limit	0.071

Secondary: Clinical measures of vision: Near visual acuity	
End point title	Clinical measures of vision: Near visual acuity

End point description:

Near visual acuity (NVA) is measured in logMAR units using charts that utilise words of specific character sizes and lengths.

End point type	Secondary
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End point timeframe:

Measured at 0, 3, 6, 12, 18 and 24 months

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: logMAR				
arithmetic mean (standard deviation)	0.55 (± 0.39)	0.61 (± 0.42)	0.58 (± 0.40)	0.58 (± 0.41)

Statistical analyses

Statistical analysis title	Near visual acuity, by drug
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Statistical analysis description:

Difference in NVA at 2 years, by drug allocation. Difference is estimated using data from visits 0, 3, 6, 12, 18 and 24, adjusted for center size. GMR values of < 1 reflect a better outcome in the ranibizumab group.

Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.23
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.04

Statistical analysis title	Near visual acuity, by treatment regimen
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Statistical analysis description:

Difference in NVA at 2 years, by treatment regimen allocation. Difference is estimated using data from visits 0, 3, 6, 12, 18 and 24, adjusted for center size. GMR values of < 1 reflect a better outcome in the continuous group.

Comparison groups	Discontinuous v Continuous
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Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.04
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	0.99

Secondary: Clinical measures of vision: Reading index

End point title	Clinical measures of vision: Reading index
End point description:	
Reading index is a derivative of reading speed. Reading speed is a psychophysical test, which measures ability to read a string of words without reference to context. It tests the ability of the eye to scan along a line of words, and this function is impaired if visual deficits are present in the parafoveal retina. Reading speed is measured using a print size subtending a visual angle that is 0.1 logMAR larger than the threshold NVA and expressed in units of words read per minute. The reading index is the reading speed divided by the size of print read and thus makes allowance for the visual angle.	
End point type	Secondary
End point timeframe:	
Measured at 0, 3, 6, 12, 18 and 24 months	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Words read				
median (inter-quartile range (Q1-Q3))	50.9 (22.8 to 93.7)	52.5 (9.7 to 90.6)	46.3 (11.4 to 84.0)	55.4 (19.0 to 97.6)

Statistical analyses

Statistical analysis title	Reading index, by drug
Statistical analysis description:	
Difference in reading index at 2 years, by drug allocation. Difference is estimated using data from visits 0, 3, 6, 12, 18 and 24, adjusted for center size. Negative values reflect a better outcome in the ranibizumab group.	
Comparison groups	Ranibizumab v Bevacizumab

Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.7
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.29
upper limit	5.61

Statistical analysis title	Reading index, by treatment regimen
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Statistical analysis description:

Difference in reading index at 2 years, by treatment regimen allocation. Difference is estimated using data from visits 0, 3, 6, 12, 18 and 24, adjusted for center size. Negative values reflect a better outcome in the continuous group.

Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.93
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.27
upper limit	6.62

Secondary: Clinical measures of vision: Contrast sensitivity

End point title	Clinical measures of vision: Contrast sensitivity
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End point description:

Contrast sensitivity is a global measure of macular function. It has been suggested that it represents a better surrogate marker for visual function than BCVA by virtue of the fact that some studies have observed better correlation with patient-reported outcomes.

End point type	Secondary
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End point timeframe:

Measured at 0, 3, 6, 12, 18 and 24 months

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Letters				
arithmetic mean (standard deviation)	28.1 (± 6.0)	28.3 (± 5.8)	28.7 (± 5.4)	27.7 (± 6.3)

Statistical analyses

Statistical analysis title	Contrast sensitivity, by drug
Statistical analysis description:	
Difference in contrast sensitivity at 2 years, by drug allocation. Difference is estimated using data from visits 0, 3, 6, 12, 18 and 24, adjusted for center size. Negative values reflect a better outcome in the ranibizumab group.	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.62
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.62
upper limit	1.04

Statistical analysis title	Contrast sensitivity, by treatment regimen
Statistical analysis description:	
Difference in contrast sensitivity at 2 years, by treatment regimen allocation. Difference is estimated using data from visits 0, 3, 6, 12, 18 and 24, adjusted for center size. Negative values reflect a better outcome in the continuous group.	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	-0.25

Secondary: Lesion morphology: Geographic atrophy

End point title	Lesion morphology: Geographic atrophy
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End point description:

New GA during follow-up in trial. Assessed from colour and FFA. Area $\geq 175 \mu\text{m}$ greatest linear dimension with two or more relevant features in colour images (well-defined margins; visibility of choroidal vessels; scalloped edges) and consistent finding on FFA (early hyperfluorescence, persisting through the FFA sequence and fading in late images)

End point type	Secondary
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End point timeframe:

During follow-up in trial. Measured at baseline, 12 and 24 months.

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients	86	91	101	76

Statistical analyses

Statistical analysis title	Geographic atrophy, by drug
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Statistical analysis description:

Ratios of < 1 reflect better outcomes in the ranibizumab group

Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.46
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.25

Statistical analysis title	Geographic atrophy, by treatment regimen
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Statistical analysis description:

Ratios of < 1 reflect better outcomes in the continuous group

Comparison groups	Continuous v Discontinuous
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Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.033
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	2.11

Secondary: Lesion morphology: Dye leakage

End point title	Lesion morphology: Dye leakage
End point description:	Dye leakage on angiogram (assessed from FFA). Areas of featureless hyperfluorescence that increase in the late frames and which may also exhibit well delineated hyperfluorescence in the early frames.
End point type	Secondary
End point timeframe:	Measured at baseline, 12 and 24 months.

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients	101	89	86	104

Statistical analyses

Statistical analysis title	Dye leakage, by drug
Statistical analysis description:	Ratios of < 1 reflect better outcomes in the ranibizumab group
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.46
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.67

Statistical analysis title	Dye leakage, by treatment regimen
Statistical analysis description:	
Ratios of < 1 reflect better outcomes in the continuous group	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.11
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.07

Secondary: Lesion morphology: Fluid

End point title	Lesion morphology: Fluid
End point description:	
Any fluid on OCT	
End point type	Secondary
End point timeframe:	
Measured at 0, 3, 6, 9, 12, 15, 18, 21 and 24 months	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients	127	141	112	156

Statistical analyses

Statistical analysis title	Fluid, by drug
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Statistical analysis description:

Ratios of < 1 reflect better outcomes in the ranibizumab group

Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.065
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.02

Statistical analysis title	Fluid, by treatment regimen
Statistical analysis description:	
Ratios of < 1 reflect better outcomes in the continuous group	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.67

Secondary: Lesion morphology: Lesion present	
End point title	Lesion morphology: Lesion present
End point description:	
Assessed from FFA	
End point type	Secondary
End point timeframe:	
Measured at baseline, 12 and 24 months.	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Patients	142	127	123	146

Statistical analyses

Statistical analysis title	Lesion present, by drug
Statistical analysis description:	
Ratios of < 1 reflect better outcomes in the ranibizumab group	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.44
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.67

Statistical analysis title	Lesion present, by treatment regimen
Statistical analysis description:	
Ratios of < 1 reflect better outcomes in the continuous group	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.024
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.95

Secondary: Lesion morphology: Retinal plus subretinal fluid thickness at fovea

End point title	Lesion morphology: Retinal plus subretinal fluid thickness at fovea
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End point description:

Assessed from OCT. Foveal neuroretinal thickness (a linear measurement of the distance between the inner and outer boundary of the neurosensory retina at the foveal centre) plus SRF thickness at fovea (height of hyporeflective region separating the RPE band from the outer boundary of the neurosensory retina at the foveal centre).

End point type	Secondary
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End point timeframe:

Measured at 0, 3, 6, 9, 12, 15, 18, 21 and 24 months.

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: μm				
arithmetic mean (standard deviation)	163.5 ($\pm$ 77.7)	172.7 ($\pm$ 95.7)	161.7 ($\pm$ 84.2)	174.4 ($\pm$ 89.4)

Statistical analyses

Statistical analysis title	Retinal plus SRF thickness, by drug
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Statistical analysis description:

Ratios of < 1 reflect better outcomes in the ranibizumab group

Comparison groups	Ranibizumab v Bevacizumab
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Number of subjects included in analysis	610
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Analysis specification	Pre-specified
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Analysis type	non-inferiority
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P-value	= 0.75
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Method	Mixed models analysis
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Parameter estimate	Geometric mean ratio
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Point estimate	0.99
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.9
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upper limit	1.08
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Statistical analysis title	Retinal plus SRF thickness, by treatment regimen
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Statistical analysis description:

Ratios of < 1 reflect better outcomes in the continuous group

Comparison groups	Continuous v Discontinuous
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Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.046
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1

Secondary: Lesion morphology: Total lesion thickness at the fovea

End point title	Lesion morphology: Total lesion thickness at the fovea
End point description:	
Assessed from OCT. Sum of foveal neuroretinal thickness (a linear measurement of the distance between the inner and outer boundary of the neurosensory retina at the foveal centre), SRF thickness at fovea (height of hyporeflective region separating the RPE band from the outer boundary of the neurosensory retina at the foveal centre) and PED (Elevation of the hyper-reflective band corresponding to the RPE and or scar at the foveal centre).	
End point type	Secondary
End point timeframe:	
Measured at 0, 3, 6, 9, 12, 15, 18, 21 and 24 months.	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: μM				
arithmetic mean (standard deviation)	322.4 ($\pm$ 137.3)	331 ($\pm$ 144.2)	314.7 ($\pm$ 137.1)	338.5 ($\pm$ 143.3)

Statistical analyses

Statistical analysis title	Total lesion thickness, by drug
Statistical analysis description:	
Ratios of < 1 reflect better outcomes in the ranibizumab group	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.24
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.03

Statistical analysis title	Total lesion thickness, by treatment regimen
Statistical analysis description:	
Ratios of < 1 reflect better outcomes in the continuous group	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0035
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	0.97

Secondary: Best corrected visual acuity at 1 year

End point title	Best corrected visual acuity at 1 year
End point description:	
Results of interim analysis: BCVA after all patients have been followed for 1 year after starting treatment.	
End point type	Secondary
End point timeframe:	
Measured at 0, 3, 6, and 12 months	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308	302
Units: Letters				
arithmetic mean (standard deviation)	69.0 (± 16.0)	66.1 (± 17.4)	66.8 (± 17.4)	68.4 (± 16.1)

Statistical analyses

Statistical analysis title	BCVA at 1 year, by drug
Statistical analysis description:	
Difference in BCVA at 1 year, by drug allocation. Difference is estimated using data from visits 0, 3, 6 and 12, adjusted for center size. Negative values reflect a better mean VA in the ranibizumab group. Non-inferiority limit = -3.5 letters	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.056
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.04
upper limit	0.06

Statistical analysis title	BCVA at 1 year, by treatment regimen
Statistical analysis description:	
Difference in BCVA at 1 year, by treatment regimen allocation. Difference is estimated using data from visits 0, 3, 6 and 12, adjusted for center size. Negative values reflect a better mean VA in the continuous group. Non-inferiority limit = -3.5 letters	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.74
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	1.7

Secondary: Survival free from treatment failure	
End point title	Survival free from treatment failure
End point description:	
Treatment failure: Satisfying one or more of the criteria for re-treatment.	
End point type	Secondary
End point timeframe:	
Re-treatment criteria collected monthly from month 3-24.	

End point values	Ranibizumab	Bevacizumab	Continuous	Discontinuous
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	314	296	308 ^[21]	302
Units: Months				
median (inter-quartile range (Q1-Q3))	5.1 (3.7 to 16.8)	4.9 (3.2 to 14.0)	7.6 (3.2 to 24.0)	4.4 (3.2 to 6.9)

Notes:

[21] - 75th percentile (Q3) not reached. Maximum duration (24 months) entered.

Statistical analyses

Statistical analysis title	Time to treatment failure, by drug
Statistical analysis description:	
Hazard ratio (bevacizumab–ranibizumab)	
Comparison groups	Ranibizumab v Bevacizumab
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.18
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.36

Statistical analysis title	Time to treatment failure, by regimen
Statistical analysis description:	
Hazard ratio (discontinuous–continuous)	
Comparison groups	Continuous v Discontinuous
Number of subjects included in analysis	610
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.61
upper limit	2.35

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events, both serious and non-serious, were recorded at each visit.

Adverse event reporting additional description:

All expected adverse events and unexpected adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA, McLean, VA, USA). All SAEs were reviewed by senior clinicians masked to treatment allocation.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.1
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Reporting groups

Reporting group title	Ranibizumab
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Reporting group description:

Intravitreal injections of ranibizumab (0.5mg), either monthly (if randomised to continuous treatment regimen) or as-needed (if randomised to discontinuous treatment regimen).

Reporting group title	Bevacizumab
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Reporting group description:

Intravitreal injections of bevacizumab (1.25mg), either monthly (if randomised to continuous treatment regimen) or as-needed (if randomised to discontinuous treatment regimen).

Reporting group title	Continuous
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Reporting group description:

Monthly treatment.

Reporting group title	Discontinuous
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Reporting group description:

Treated if pre specified clinical and OCT criteria for active disease were met. If re-treatment was needed, a further cycle of three doses was given monthly.

Serious adverse events	Ranibizumab	Bevacizumab	Continuous
Total subjects affected by serious adverse events			
subjects affected / exposed	87 / 314 (27.71%)	84 / 296 (28.38%)	79 / 308 (25.65%)
number of deaths (all causes)	15	15	10
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Bladder transitional cell carcinoma			

subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Breast cancer			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Colon cancer			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Gallbladder cancer			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 314 (0.00%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic neoplasm malignant			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	5 / 314 (1.59%)	2 / 296 (0.68%)	3 / 308 (0.97%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Mantle cell lymphoma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Mesothelioma			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	2 / 314 (0.64%)	1 / 296 (0.34%)	3 / 308 (0.97%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 3
Oesophageal carcinoma			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cancer			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Pancreatic carcinoma			
subjects affected / exposed	0 / 314 (0.00%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Prostate cancer metastatic			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Haematoma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	3 / 314 (0.96%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	2 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Poor peripheral circulation			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Surgical and medical procedures			
Analgesic therapy			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Aortic aneurysm repair			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac pacemaker insertion			

subjects affected / exposed	2 / 314 (0.64%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract operation			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chemotherapy			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Cholecystectomy			
subjects affected / exposed	0 / 314 (0.00%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithotomy			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Cochlea implant			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery bypass			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterostomy			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrostomy tube insertion			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Hip arthroplasty			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hospitalisation			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hysterectomy			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee arthroplasty			
subjects affected / exposed	1 / 314 (0.32%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Knee operation			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung lobectomy			
subjects affected / exposed	2 / 314 (0.64%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastectomy			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Peripheral nerve operation			

subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Sebacous cyst excision			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Skin neoplasm excision			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Surgery			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Transurethral bladder resection			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transurethral prostatectomy			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Vulval operation			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	15 / 314 (4.78%)	15 / 296 (5.07%)	10 / 308 (3.25%)
occurrences causally related to treatment / all	4 / 15	3 / 15	2 / 10
deaths causally related to treatment / all	4 / 15	3 / 15	2 / 10
Multi-organ failure			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Swelling			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Hypersensitivity			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Convalescent			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 314 (0.64%)	0 / 296 (0.00%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Pulmonary embolism			
subjects affected / exposed	3 / 314 (0.96%)	3 / 296 (1.01%)	3 / 308 (0.97%)
occurrences causally related to treatment / all	1 / 3	1 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	1 / 1	1 / 1
Pulmonary oedema			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Investigations			
Biopsy			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Biopsy vulva			

subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endoscopy upper gastrointestinal tract			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
IOP increased			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	7 / 314 (2.23%)	2 / 296 (0.68%)	3 / 308 (0.97%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stoma complication			

subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	1 / 314 (0.32%)	3 / 296 (1.01%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint dislocation			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Multiple fractures			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Pelvic fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	2 / 314 (0.64%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Wrist fracture			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	7 / 314 (2.23%)	3 / 296 (1.01%)	6 / 308 (1.95%)
occurrences causally related to treatment / all	4 / 7	2 / 3	3 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 314 (0.32%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 314 (0.00%)	3 / 296 (1.01%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Cardiac failure			
subjects affected / exposed	7 / 314 (2.23%)	2 / 296 (0.68%)	5 / 308 (1.62%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Mitral valve incompetence			

subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
MI			
subjects affected / exposed	4 / 314 (1.27%)	4 / 296 (1.35%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	4 / 4	3 / 5	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial haemorrhage			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 314 (0.00%)	2 / 296 (0.68%)	0 / 308 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	7 / 314 (2.23%)	3 / 296 (1.01%)	4 / 308 (1.30%)
occurrences causally related to treatment / all	6 / 7	2 / 3	3 / 4
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Facial paresis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Frontotemporal dementia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Presyncope			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Unresponsive to stimuli			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Thrombocytopenia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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			
Meniere's disease			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Sudden hearing loss			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Amaurosis fugax			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Blindness			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract traumatic			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Keratitis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Retinal detachment			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Retinal haemorrhage			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RPE tear			
subjects affected / exposed	3 / 314 (0.96%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion			

subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Non-study eye: AMD			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-study eye: Cataract			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Non-study eye: Endophthalmitis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-study eye: Herpes zoster			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Non-study eye: Wound evisceration			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	2 / 314 (0.64%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Colitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Crohn's disease			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Intestinal obstruction			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Intestinal perforation			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Pancreatitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis chronic			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Vomiting			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Cholelithiasis			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary bladder polyp			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	2 / 314 (0.64%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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			
Abdominal infection			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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

Cholecystitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (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
Gastroenteritis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Lower respiratory tract infection			
subjects affected / exposed	4 / 314 (1.27%)	5 / 296 (1.69%)	5 / 308 (1.62%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 314 (0.96%)	5 / 296 (1.69%)	3 / 308 (0.97%)
occurrences causally related to treatment / all	1 / 3	0 / 5	0 / 3
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 1
Upper respiratory tract infection			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 314 (0.32%)	2 / 296 (0.68%)	3 / 308 (0.97%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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
Hyponatraemia			

subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (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

Serious adverse events	Discontinuous		
Total subjects affected by serious adverse events			
subjects affected / exposed	92 / 302 (30.46%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Colon cancer			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Gallbladder cancer			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal carcinoma			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatic neoplasm malignant subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lung neoplasm malignant subjects affected / exposed	4 / 302 (1.32%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 2			
Mantle cell lymphoma subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mesothelioma subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastatic neoplasm subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal carcinoma subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ovarian cancer subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pancreatic carcinoma subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				

subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer metastatic			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Orthostatic hypotension			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Poor peripheral circulation			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vasculitis			

subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Analgesic therapy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aortic aneurysm repair			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cataract operation			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chemotherapy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystectomy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithotomy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cochlea implant			

subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery bypass			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enterostomy			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrostomy tube insertion			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hip arthroplasty			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hospitalisation			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hysterectomy			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Knee arthroplasty			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Knee operation			

subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung lobectomy			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mastectomy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral nerve operation			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sebaceous cyst excision			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin neoplasm excision			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgery			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transurethral bladder resection			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transurethral prostatectomy			

subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vulval operation			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	20 / 302 (6.62%)		
occurrences causally related to treatment / all	5 / 20		
deaths causally related to treatment / all	5 / 20		
Multi-organ failure			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Swelling			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Convalescent			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Emphysema			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nasal polyps			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			

subjects affected / exposed	3 / 302 (0.99%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Investigations			
Biopsy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Biopsy vulva			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endoscopy upper gastrointestinal tract			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
IOP increased			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clavicle fracture			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Fall				
subjects affected / exposed	6 / 302 (1.99%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal stoma complication				
subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	2 / 302 (0.66%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Joint dislocation				
subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple fractures				
subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				

subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Upper limb fracture			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 2		
Cardiac failure			

subjects affected / exposed	4 / 302 (1.32%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Cor pulmonale			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Left ventricular failure			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mitral valve incompetence			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
MI			
subjects affected / exposed	6 / 302 (1.99%)		
occurrences causally related to treatment / all	5 / 7		
deaths causally related to treatment / all	0 / 0		
Palpitations			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pericardial haemorrhage			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Supraventricular tachycardia			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	6 / 302 (1.99%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	1 / 1		
Facial paresis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Frontotemporal dementia			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Unresponsive to stimuli			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Microcytic anaemia			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			

subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden hearing loss			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blindness			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cataract traumatic			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diplopia			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Keratitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment			

subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal haemorrhage				
subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
RPE tear				
subjects affected / exposed	2 / 302 (0.66%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Retinal vein occlusion				
subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uveitis				
subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage				
subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-study eye: AMD				
subjects affected / exposed	0 / 302 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-study eye: Cataract				
subjects affected / exposed	1 / 302 (0.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-study eye: Endophthalmitis				

subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-study eye: Herpes zoster			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-study eye: Wound evisceration			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Crohn's disease			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspepsia			

subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Faecaloma			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal perforation			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis chronic			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			

subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary bladder polyp			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal pain			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Localised infection			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 1		
Pneumonia			
subjects affected / exposed	5 / 302 (1.66%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	1 / 1		
Upper respiratory tract infection			

subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Ranibizumab	Bevacizumab	Continuous
Total subjects affected by non-serious adverse events			
subjects affected / exposed	294 / 314 (93.63%)	276 / 296 (93.24%)	289 / 308 (93.83%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	15 / 314 (4.78%)	9 / 296 (3.04%)	11 / 308 (3.57%)
occurrences (all)	15	10	12
Vascular disorders			
Vascular disorders			
subjects affected / exposed	55 / 314 (17.52%)	51 / 296 (17.23%)	58 / 308 (18.83%)
occurrences (all)	72	66	79
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	19 / 314 (6.05%)	15 / 296 (5.07%)	13 / 308 (4.22%)
occurrences (all)	23	16	14
General disorders and administration			

site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	40 / 314 (12.74%) 52	49 / 296 (16.55%) 61	46 / 308 (14.94%) 56
Immune system disorders Immune system disorders subjects affected / exposed occurrences (all)	10 / 314 (3.18%) 10	7 / 296 (2.36%) 8	9 / 308 (2.92%) 10
Social circumstances Social circumstances subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Reproductive system and breast disorders Reproductive system and breast disorders subjects affected / exposed occurrences (all)	6 / 314 (1.91%) 7	7 / 296 (2.36%) 7	3 / 308 (0.97%) 3
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	125 / 314 (39.81%) 218	122 / 296 (41.22%) 199	119 / 308 (38.64%) 199
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	10 / 314 (3.18%) 14	10 / 296 (3.38%) 11	13 / 308 (4.22%) 17
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 3	1 / 296 (0.34%) 1	1 / 308 (0.32%) 1
Investigations Investigation subjects affected / exposed occurrences (all)	18 / 314 (5.73%) 21	24 / 296 (8.11%) 28	19 / 308 (6.17%) 22
Injury, poisoning and procedural complications Accident subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	1 / 296 (0.34%) 1	1 / 308 (0.32%) 1

Animal bite			
subjects affected / exposed	2 / 314 (0.64%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences (all)	2	1	2
Ankle fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Arthropod bite			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences (all)	1	2	3
Cartilage injury			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	11 / 314 (3.50%)	3 / 296 (1.01%)	10 / 308 (3.25%)
occurrences (all)	13	3	12
Epicondylitis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Excoriation			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Eye injury			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Face injury			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Fall			
subjects affected / exposed	31 / 314 (9.87%)	27 / 296 (9.12%)	31 / 308 (10.06%)
occurrences (all)	40	37	40
Foot fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Foreign body			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0

Fracture			
subjects affected / exposed	2 / 314 (0.64%)	6 / 296 (2.03%)	2 / 308 (0.65%)
occurrences (all)	3	6	2
Hand fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
injury			
subjects affected / exposed	2 / 314 (0.64%)	3 / 296 (1.01%)	2 / 308 (0.65%)
occurrences (all)	2	3	2
Joint dislocation			
subjects affected / exposed	2 / 314 (0.64%)	2 / 296 (0.68%)	2 / 308 (0.65%)
occurrences (all)	2	2	2
Joint injury			
subjects affected / exposed	2 / 314 (0.64%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	2	0	1
Joint sprain			
subjects affected / exposed	4 / 314 (1.27%)	3 / 296 (1.01%)	2 / 308 (0.65%)
occurrences (all)	4	3	2
Laceration			
subjects affected / exposed	5 / 314 (1.59%)	3 / 296 (1.01%)	4 / 308 (1.30%)
occurrences (all)	6	3	5
Ligament sprain			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Limb injury			
subjects affected / exposed	7 / 314 (2.23%)	5 / 296 (1.69%)	9 / 308 (2.92%)
occurrences (all)	7	5	9
Mouth injury			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Muscle strain			
subjects affected / exposed	4 / 314 (1.27%)	3 / 296 (1.01%)	4 / 308 (1.30%)
occurrences (all)	4	3	4
Rib fracture			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0

Road traffic accident subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Thermal burn subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 3	0 / 296 (0.00%) 0	0 / 308 (0.00%) 0
Vascular injury subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 2	0 / 296 (0.00%) 0	2 / 308 (0.65%) 2
Congenital, familial and genetic disorders Congenital, familial and genetic disorders subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	4 / 314 (1.27%) 5	4 / 296 (1.35%) 4	4 / 308 (1.30%) 4
Arrhythmia subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	1 / 308 (0.32%) 1
Atrial fibrillation subjects affected / exposed occurrences (all)	4 / 314 (1.27%) 4	4 / 296 (1.35%) 4	4 / 308 (1.30%) 4
Bradycardia subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	0 / 308 (0.00%) 0
Cardiac disorder subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	1 / 308 (0.32%) 1
Cardiac flutter subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	2 / 296 (0.68%) 2	2 / 308 (0.65%) 2
Cardiac valve disease subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	1 / 308 (0.32%) 1
Mitral valve incompetence			

subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 4	0 / 296 (0.00%) 0	2 / 308 (0.65%) 4
Supraventricular tachycardia subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Tachycardia subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	90 / 314 (28.66%) 157	77 / 296 (26.01%) 108	76 / 308 (24.68%) 121
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	5 / 314 (1.59%) 5	10 / 296 (3.38%) 11	12 / 308 (3.90%) 13
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	18 / 314 (5.73%) 23	20 / 296 (6.76%) 23	21 / 308 (6.82%) 26
Eye disorders Abnormal sensation in eye subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	0 / 308 (0.00%) 0
Blepharitis subjects affected / exposed occurrences (all)	9 / 314 (2.87%) 9	10 / 296 (3.38%) 15	10 / 308 (3.25%) 12
Blepharoplasty subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	1 / 308 (0.32%) 1
Blepharospasm subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 2	1 / 296 (0.34%) 1	1 / 308 (0.32%) 1

Cataract			
subjects affected / exposed	7 / 314 (2.23%)	7 / 296 (2.36%)	8 / 308 (2.60%)
occurrences (all)	7	7	8
Cataract cortical			
subjects affected / exposed	3 / 314 (0.96%)	1 / 296 (0.34%)	3 / 308 (0.97%)
occurrences (all)	3	1	3
Cataract nuclear			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Cataract operation			
subjects affected / exposed	3 / 314 (0.96%)	5 / 296 (1.69%)	7 / 308 (2.27%)
occurrences (all)	3	6	8
Cataract traumatic			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Chalazion			
subjects affected / exposed	2 / 314 (0.64%)	4 / 296 (1.35%)	3 / 308 (0.97%)
occurrences (all)	2	5	3
Colour blindness acquired			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Conjunctival cyst			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Conjunctival haemorrhage			
subjects affected / exposed	59 / 314 (18.79%)	56 / 296 (18.92%)	67 / 308 (21.75%)
occurrences (all)	77	72	86
Conjunctival hyperaemia			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Conjunctivitis			
subjects affected / exposed	8 / 314 (2.55%)	8 / 296 (2.70%)	9 / 308 (2.92%)
occurrences (all)	9	9	11
Conjunctivitis allergic			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0

Corneal abrasion			
subjects affected / exposed	8 / 314 (2.55%)	10 / 296 (3.38%)	12 / 308 (3.90%)
occurrences (all)	13	11	16
Corneal deposits			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Corneal disorder			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Corneal dystrophy			
subjects affected / exposed	2 / 314 (0.64%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	2	0	1
Corneal erosion			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Corneal perforation			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Dacryocystitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Diplopia			
subjects affected / exposed	4 / 314 (1.27%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences (all)	4	2	1
Dry eye			
subjects affected / exposed	10 / 314 (3.18%)	4 / 296 (1.35%)	8 / 308 (2.60%)
occurrences (all)	13	5	9
Episcleritis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Exophthalmos			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Eye discharge			
subjects affected / exposed	8 / 314 (2.55%)	2 / 296 (0.68%)	5 / 308 (1.62%)
occurrences (all)	9	4	7

Eye haemorrhage			
subjects affected / exposed	0 / 314 (0.00%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences (all)	0	2	1
Eye infection			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Eye inflammation			
subjects affected / exposed	3 / 314 (0.96%)	6 / 296 (2.03%)	3 / 308 (0.97%)
occurrences (all)	3	9	3
Eye irritation			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Eye pain			
subjects affected / exposed	91 / 314 (28.98%)	91 / 296 (30.74%)	97 / 308 (31.49%)
occurrences (all)	146	150	166
Eye pruritus			
subjects affected / exposed	2 / 314 (0.64%)	2 / 296 (0.68%)	2 / 308 (0.65%)
occurrences (all)	2	3	2
Eye swelling			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Eyelid cyst			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences (all)	1	1	2
Eyelid irritation			
subjects affected / exposed	0 / 314 (0.00%)	2 / 296 (0.68%)	0 / 308 (0.00%)
occurrences (all)	0	2	0
Eyelid oedema			
subjects affected / exposed	0 / 314 (0.00%)	4 / 296 (1.35%)	1 / 308 (0.32%)
occurrences (all)	0	4	1
Eyelid pain			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Eyelid ptosis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1

Fibrosis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Foreign body sensation in eyes			
subjects affected / exposed	3 / 314 (0.96%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	3	0	1
Glaucoma			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	1	1	1
Glaucomatous optic disc atrophy			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Hallucination, visual			
subjects affected / exposed	8 / 314 (2.55%)	2 / 296 (0.68%)	5 / 308 (1.62%)
occurrences (all)	8	2	5
Hordeolum			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	1	1	1
Intraocular lens implant			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
IOP increased			
subjects affected / exposed	79 / 314 (25.16%)	66 / 296 (22.30%)	87 / 308 (28.25%)
occurrences (all)	154	130	188
Iridocyclitis			
subjects affected / exposed	0 / 314 (0.00%)	2 / 296 (0.68%)	0 / 308 (0.00%)
occurrences (all)	0	2	0
Iridotomy			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Keratitis			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	2	1	2
Lacrimal mucocoele			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0

Lacrimation increased			
subjects affected / exposed	30 / 314 (9.55%)	41 / 296 (13.85%)	35 / 308 (11.36%)
occurrences (all)	37	53	43
Laser therapy			
subjects affected / exposed	2 / 314 (0.64%)	2 / 296 (0.68%)	2 / 308 (0.65%)
occurrences (all)	2	2	2
Lenticular opacities			
subjects affected / exposed	2 / 314 (0.64%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences (all)	2	1	2
Macular oedema			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Maculopathy			
subjects affected / exposed	0 / 314 (0.00%)	2 / 296 (0.68%)	0 / 308 (0.00%)
occurrences (all)	0	2	0
Metamorphopsia			
subjects affected / exposed	2 / 314 (0.64%)	3 / 296 (1.01%)	2 / 308 (0.65%)
occurrences (all)	3	3	2
Mydriasis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Optic disc haemorrhage			
subjects affected / exposed	3 / 314 (0.96%)	1 / 296 (0.34%)	3 / 308 (0.97%)
occurrences (all)	3	1	3
Paracentesis eye			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Periorbital haematoma			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Photophobia			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences (all)	1	1	2
Photopsia			
subjects affected / exposed	2 / 314 (0.64%)	3 / 296 (1.01%)	5 / 308 (1.62%)
occurrences (all)	2	3	5

Pigment dispersion syndrome subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	0 / 308 (0.00%) 0
Posterior capsule opacification subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	2 / 296 (0.68%) 2	1 / 308 (0.32%) 1
Posterior capsulotomy subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 2	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Punctate keratitis subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Pupillary reflex impaired subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 2	0 / 296 (0.00%) 0	1 / 308 (0.32%) 2
Retinal artery embolism subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Retinal artery occlusion subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	1 / 308 (0.32%) 1
Retinal artery spasm subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	0 / 308 (0.00%) 0
Retinal detachment subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	0 / 308 (0.00%) 0
Retinal haemorrhage subjects affected / exposed occurrences (all)	8 / 314 (2.55%) 10	15 / 296 (5.07%) 16	10 / 308 (3.25%) 12
Retinal oedema subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 2	3 / 296 (1.01%) 3	0 / 308 (0.00%) 0
RPE tear subjects affected / exposed occurrences (all)	5 / 314 (1.59%) 5	2 / 296 (0.68%) 2	3 / 308 (0.97%) 3

Retinal tear			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Retinal vein occlusion			
subjects affected / exposed	3 / 314 (0.96%)	3 / 296 (1.01%)	3 / 308 (0.97%)
occurrences (all)	3	3	3
Skin lesion excision			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Superficial injury of eye			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Uveitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Vascular occlusion			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Vision blurred			
subjects affected / exposed	5 / 314 (1.59%)	6 / 296 (2.03%)	6 / 308 (1.95%)
occurrences (all)	5	6	6
Visual acuity reduced			
subjects affected / exposed	4 / 314 (1.27%)	3 / 296 (1.01%)	1 / 308 (0.32%)
occurrences (all)	5	3	1
Visual field defect			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	14 / 314 (4.46%)	17 / 296 (5.74%)	14 / 308 (4.55%)
occurrences (all)	17	17	14
Vitreous cells			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Vitreous adhesions			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0

Vitreous detachment subjects affected / exposed occurrences (all)	19 / 314 (6.05%) 19	14 / 296 (4.73%) 15	16 / 308 (5.19%) 17
Vitreous disorder subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Vitreous floaters subjects affected / exposed occurrences (all)	65 / 314 (20.70%) 81	60 / 296 (20.27%) 74	71 / 308 (23.05%) 88
Vitreous haemorrhage subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Non-study eye: Cataract subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	0 / 308 (0.00%) 0
Non-study eye: Cataract operation subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	4 / 296 (1.35%) 4	1 / 308 (0.32%) 1
Non-study eye: CNV subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	2 / 296 (0.68%) 2	1 / 308 (0.32%) 1
Non-study eye: Conjunctivitis subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 2	0 / 296 (0.00%) 0	1 / 308 (0.32%) 1
Non-study eye: Corneal abrasion subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	1 / 308 (0.32%) 1
Non-study eye: Eye inflammation subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	1 / 308 (0.32%) 1
Non-study eye: Eye irritation subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Non-study eye: Macular degeneration			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Non-study eye: Metamorphopsia			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Non-study eye: Ocular hyperaemia			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Non-study eye: Retinal artery embolism			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Non-study eye: Retinal haemorrhage			
subjects affected / exposed	2 / 314 (0.64%)	1 / 296 (0.34%)	2 / 308 (0.65%)
occurrences (all)	2	1	2
Non-study eye: RPE tear			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Non-study eye: Venous stasis retinopathy			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Non-study eye: Vision blurred			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Non-study eye: Visual acuity reduced			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 314 (0.64%)	4 / 296 (1.35%)	2 / 308 (0.65%)
occurrences (all)	2	4	2
Abdominal distension			
subjects affected / exposed	2 / 314 (0.64%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	2	0	1
Abdominal hernia			

subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Abdominal pain			
subjects affected / exposed	2 / 314 (0.64%)	5 / 296 (1.69%)	5 / 308 (1.62%)
occurrences (all)	2	5	5
Abdominal pain upper			
subjects affected / exposed	5 / 314 (1.59%)	3 / 296 (1.01%)	6 / 308 (1.95%)
occurrences (all)	7	3	8
Abdominal symptom			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Anal fissure			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Anorectal discomfort			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Change of bowel habit			
subjects affected / exposed	2 / 314 (0.64%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	2	0	1
Colitis			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Colitis ulcerative			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	4 / 314 (1.27%)	7 / 296 (2.36%)	6 / 308 (1.95%)
occurrences (all)	4	7	6
Crohn's disease			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	23 / 314 (7.32%)	13 / 296 (4.39%)	15 / 308 (4.87%)
occurrences (all)	28	13	17
Dry mouth			

subjects affected / exposed	1 / 314 (0.32%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences (all)	1	2	1
Dyspepsia			
subjects affected / exposed	3 / 314 (0.96%)	5 / 296 (1.69%)	4 / 308 (1.30%)
occurrences (all)	3	5	4
Dysphagia lusoria			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	1	1	1
Faecal incontinence			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Faecal vomiting			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Food poisoning			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	1	1	1
Gastric disorder			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	1	1	1
Gastritis			
subjects affected / exposed	1 / 314 (0.32%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	1	1	1
Gastro-oesophageal reflux disease			
subjects affected / exposed	0 / 314 (0.00%)	3 / 296 (1.01%)	2 / 308 (0.65%)
occurrences (all)	0	3	2
Gingival disorder			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Gingival pain			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Glossitis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Haemorrhoids			

subjects affected / exposed	2 / 314 (0.64%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	2	1	0
Hiatus hernia			
subjects affected / exposed	2 / 314 (0.64%)	3 / 296 (1.01%)	4 / 308 (1.30%)
occurrences (all)	2	3	4
Intestinal obstruction			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Irritable bowel syndrome			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	3	0	3
Lip swelling			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Mouth ulceration			
subjects affected / exposed	4 / 314 (1.27%)	2 / 296 (0.68%)	4 / 308 (1.30%)
occurrences (all)	4	2	4
Nausea			
subjects affected / exposed	38 / 314 (12.10%)	27 / 296 (9.12%)	31 / 308 (10.06%)
occurrences (all)	51	36	46
Oedema mouth			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	1 / 308 (0.32%)
occurrences (all)	1	0	1
Oesophagitis			
subjects affected / exposed	1 / 314 (0.32%)	0 / 296 (0.00%)	0 / 308 (0.00%)
occurrences (all)	1	0	0
Pancreatic cyst			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	1 / 308 (0.32%)
occurrences (all)	0	1	1
Pancreatitis acute			
subjects affected / exposed	0 / 314 (0.00%)	1 / 296 (0.34%)	0 / 308 (0.00%)
occurrences (all)	0	1	0
Rectal haemorrhage			
subjects affected / exposed	1 / 314 (0.32%)	2 / 296 (0.68%)	1 / 308 (0.32%)
occurrences (all)	1	2	1
Rectal lesion			

subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	1 / 308 (0.32%) 1
Rectal prolapse subjects affected / exposed occurrences (all)	2 / 314 (0.64%) 2	0 / 296 (0.00%) 0	0 / 308 (0.00%) 0
Regurgitation subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Sensitivity of teeth subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	0 / 296 (0.00%) 0	1 / 308 (0.32%) 1
Toothache subjects affected / exposed occurrences (all)	3 / 314 (0.96%) 3	1 / 296 (0.34%) 1	2 / 308 (0.65%) 2
Vomiting subjects affected / exposed occurrences (all)	8 / 314 (2.55%) 11	5 / 296 (1.69%) 5	9 / 308 (2.92%) 12
Gingivitis subjects affected / exposed occurrences (all)	0 / 314 (0.00%) 0	1 / 296 (0.34%) 1	0 / 308 (0.00%) 0
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	38 / 314 (12.10%) 46	41 / 296 (13.85%) 47	38 / 308 (12.34%) 43
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	9 / 314 (2.87%) 10	12 / 296 (4.05%) 15	8 / 308 (2.60%) 11
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	1 / 314 (0.32%) 1	6 / 296 (2.03%) 7	3 / 308 (0.97%) 4
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders			

subjects affected / exposed occurrences (all)	91 / 314 (28.98%) 124	99 / 296 (33.45%) 144	88 / 308 (28.57%) 118
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	194 / 314 (61.78%) 448	165 / 296 (55.74%) 389	167 / 308 (54.22%) 401
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	14 / 314 (4.46%) 20	8 / 296 (2.70%) 8	12 / 308 (3.90%) 15

Non-serious adverse events	Discontinuous		
Total subjects affected by non-serious adverse events subjects affected / exposed	281 / 302 (93.05%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Neoplasms benign, malignant and unspecified subjects affected / exposed occurrences (all)	13 / 302 (4.30%) 13		
Vascular disorders Vascular disorders subjects affected / exposed occurrences (all)	48 / 302 (15.89%) 59		
Surgical and medical procedures Surgical and medical procedures subjects affected / exposed occurrences (all)	21 / 302 (6.95%) 25		
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	43 / 302 (14.24%) 57		
Immune system disorders Immune system disorders subjects affected / exposed occurrences (all)	8 / 302 (2.65%) 8		
Social circumstances			

Social circumstances subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		
Reproductive system and breast disorders Reproductive system and breast disorders subjects affected / exposed occurrences (all)	10 / 302 (3.31%) 11		
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	128 / 302 (42.38%) 218		
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	7 / 302 (2.32%) 8		
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	2 / 302 (0.66%) 3		
Investigations Investigation subjects affected / exposed occurrences (all)	23 / 302 (7.62%) 27		
Injury, poisoning and procedural complications Accident subjects affected / exposed occurrences (all) Animal bite subjects affected / exposed occurrences (all) Ankle fracture subjects affected / exposed occurrences (all) Arthropod bite	1 / 302 (0.33%) 1 1 / 302 (0.33%) 1 0 / 302 (0.00%) 0		

subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Cartilage injury			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences (all)	4		
Epicondylitis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Excoriation			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Eye injury			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Face injury			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	27 / 302 (8.94%)		
occurrences (all)	37		
Foot fracture			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Foreign body			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Fracture			
subjects affected / exposed	6 / 302 (1.99%)		
occurrences (all)	7		
Hand fracture			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
injury			

subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	3		
Joint dislocation			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Joint injury			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Joint sprain			
subjects affected / exposed	5 / 302 (1.66%)		
occurrences (all)	5		
Laceration			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences (all)	4		
Ligament sprain			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	3		
Mouth injury			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Muscle strain			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	3		
Rib fracture			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Road traffic accident			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Thermal burn			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	3		
Vascular injury			

subjects affected / exposed occurrences (all)	0 / 302 (0.00%) 0		
Congenital, familial and genetic disorders Congenital, familial and genetic disorders subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		
Cardiac disorders Angina pectoris subjects affected / exposed occurrences (all)	4 / 302 (1.32%) 5		
Arrhythmia subjects affected / exposed occurrences (all)	0 / 302 (0.00%) 0		
Atrial fibrillation subjects affected / exposed occurrences (all)	4 / 302 (1.32%) 4		
Bradycardia subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		
Cardiac disorder subjects affected / exposed occurrences (all)	0 / 302 (0.00%) 0		
Cardiac flutter subjects affected / exposed occurrences (all)	0 / 302 (0.00%) 0		
Cardiac valve disease subjects affected / exposed occurrences (all)	0 / 302 (0.00%) 0		
Mitral valve incompetence subjects affected / exposed occurrences (all)	2 / 302 (0.66%) 2		
Palpitations subjects affected / exposed occurrences (all)	0 / 302 (0.00%) 0		
Supraventricular tachycardia			

subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		
Tachycardia subjects affected / exposed occurrences (all)	2 / 302 (0.66%) 2		
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	91 / 302 (30.13%) 144		
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	3 / 302 (0.99%) 3		
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	17 / 302 (5.63%) 20		
Eye disorders Abnormal sensation in eye subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		
Blepharitis subjects affected / exposed occurrences (all)	9 / 302 (2.98%) 12		
Blepharoplasty subjects affected / exposed occurrences (all)	0 / 302 (0.00%) 0		
Blepharospasm subjects affected / exposed occurrences (all)	2 / 302 (0.66%) 2		
Cataract subjects affected / exposed occurrences (all)	6 / 302 (1.99%) 6		
Cataract cortical subjects affected / exposed occurrences (all)	1 / 302 (0.33%) 1		

Cataract nuclear			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Cataract operation			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Cataract traumatic			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Chalazion			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	4		
Colour blindness acquired			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Conjunctival cyst			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Conjunctival haemorrhage			
subjects affected / exposed	48 / 302 (15.89%)		
occurrences (all)	63		
Conjunctival hyperaemia			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	7 / 302 (2.32%)		
occurrences (all)	7		
Conjunctivitis allergic			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Corneal abrasion			
subjects affected / exposed	6 / 302 (1.99%)		
occurrences (all)	8		
Corneal deposits			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		

Corneal disorder			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Corneal dystrophy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Corneal erosion			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Corneal perforation			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Dacryocystitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Diplopia			
subjects affected / exposed	5 / 302 (1.66%)		
occurrences (all)	5		
Dry eye			
subjects affected / exposed	6 / 302 (1.99%)		
occurrences (all)	9		
Episcleritis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Exophthalmos			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Eye discharge			
subjects affected / exposed	5 / 302 (1.66%)		
occurrences (all)	6		
Eye haemorrhage			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Eye infection			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		

Eye inflammation			
subjects affected / exposed	6 / 302 (1.99%)		
occurrences (all)	9		
Eye irritation			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Eye pain			
subjects affected / exposed	85 / 302 (28.15%)		
occurrences (all)	130		
Eye pruritus			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	3		
Eye swelling			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Eyelid cyst			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Eyelid irritation			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Eyelid oedema			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	3		
Eyelid pain			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Eyelid ptosis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Fibrosis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Foreign body sensation in eyes			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		

Glaucoma			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Glaucomatous optic disc atrophy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Hallucination, visual			
subjects affected / exposed	5 / 302 (1.66%)		
occurrences (all)	5		
Hordeolum			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Intraocular lens implant			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
IOP increased			
subjects affected / exposed	58 / 302 (19.21%)		
occurrences (all)	96		
Iridocyclitis			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Iridotomy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Keratitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Lacrimal mucocoele			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	36 / 302 (11.92%)		
occurrences (all)	47		
Laser therapy			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		

Lenticular opacities			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Macular oedema			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Maculopathy			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Metamorphopsia			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	4		
Mydriasis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Optic disc haemorrhage			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Paracentesis eye			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Periorbital haematoma			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Photophobia			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Photopsia			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Pigment dispersion syndrome			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Posterior capsule opacification			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		

Posterior capsulotomy			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	3		
Punctate keratitis			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Pupillary reflex impaired			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Retinal artery embolism			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Retinal artery occlusion			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Retinal artery spasm			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Retinal detachment			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Retinal haemorrhage			
subjects affected / exposed	13 / 302 (4.30%)		
occurrences (all)	14		
Retinal oedema			
subjects affected / exposed	5 / 302 (1.66%)		
occurrences (all)	5		
RPE tear			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences (all)	4		
Retinal tear			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Retinal vein occlusion			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	3		

Skin lesion excision			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Superficial injury of eye			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Uveitis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Vascular occlusion			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	5 / 302 (1.66%)		
occurrences (all)	5		
Visual acuity reduced			
subjects affected / exposed	6 / 302 (1.99%)		
occurrences (all)	7		
Visual field defect			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Visual impairment			
subjects affected / exposed	17 / 302 (5.63%)		
occurrences (all)	20		
Vitreous cells			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Vitreous adhesions			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Vitreous detachment			
subjects affected / exposed	17 / 302 (5.63%)		
occurrences (all)	17		
Vitreous disorder			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		

Vitreous floaters			
subjects affected / exposed	54 / 302 (17.88%)		
occurrences (all)	67		
Vitreous haemorrhage			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Cataract			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Cataract operation			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	3		
Non-study eye: CNV			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Non-study eye: Conjunctivitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Corneal abrasion			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Non-study eye: Eye inflammation			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Non-study eye: Eye irritation			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Macular degeneration			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Metamorphopsia			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Non-study eye: Ocular hyperaemia			

subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Retinal artery embolism			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Retinal haemorrhage			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: RPE tear			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Venous stasis retinopathy			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Vision blurred			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Non-study eye: Visual acuity reduced			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences (all)	4		
Abdominal distension			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Abdominal hernia			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Abdominal pain upper			

subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Abdominal symptom			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Anal fissure			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Anorectal discomfort			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Change of bowel habit			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Colitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Colitis ulcerative			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	5 / 302 (1.66%)		
occurrences (all)	5		
Crohn's disease			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	21 / 302 (6.95%)		
occurrences (all)	24		
Dry mouth			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences (all)	4		
Dysphagia lusoria			

subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Faecal incontinence			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Faecal vomiting			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Food poisoning			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Gastric disorder			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Gastro-oesophageal reflux disease			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Gingival disorder			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Gingival pain			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Glossitis			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	3 / 302 (0.99%)		
occurrences (all)	3		
Hiatus hernia			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Intestinal obstruction			

subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Lip swelling			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	34 / 302 (11.26%)		
occurrences (all)	41		
Oedema mouth			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Oesophagitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Pancreatic cyst			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Pancreatitis acute			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Rectal lesion			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Rectal prolapse			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Regurgitation			

subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Sensitivity of teeth			
subjects affected / exposed	0 / 302 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	2 / 302 (0.66%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences (all)	4		
Gingivitis			
subjects affected / exposed	1 / 302 (0.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	41 / 302 (13.58%)		
occurrences (all)	50		
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	13 / 302 (4.30%)		
occurrences (all)	14		
Endocrine disorders			
Endocrine disorders			
subjects affected / exposed	4 / 302 (1.32%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	102 / 302 (33.77%)		
occurrences (all)	150		
Infections and infestations			
Infections and infestations			
subjects affected / exposed	192 / 302 (63.58%)		
occurrences (all)	436		
Metabolism and nutrition disorders			

Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	10 / 302 (3.31%) 13		
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More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2007	Amendment to study protocol: Method of masking updated.
27 March 2008	Amendments to study protocol: - Clarified that the injector will be an ophthalmologist. - Footnote added to figure 3 for clarity - Patients with 8 or more dioptres of myopia added as a exclusion criteria. - Heart failure added as a serious adverse event. - Exploratory analysis to investigate the association between serum markers and cardiovascular SAEs added. - Typographical errors in the list of systemic adverse events corrected. - The reference to feeding patient responses to the MacDQoL and the MacTSQ back to the clinic staff removed.
03 August 2010	Amendment to study protocol: - Additional blood samples to be taken for genetic analysis - Retinal pigment epithelial tear added as an ocular adverse event.
24 February 2011	Amendments to study protocol: Additional blood samples 6 & 18 months.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22578446>

<http://www.ncbi.nlm.nih.gov/pubmed/23870813>

<http://www.ncbi.nlm.nih.gov/pubmed/25220133>

<http://www.ncbi.nlm.nih.gov/pubmed/24070809>

<http://www.ncbi.nlm.nih.gov/pubmed/25079928>

<http://www.ncbi.nlm.nih.gov/pubmed/26445075>

<http://www.ncbi.nlm.nih.gov/pubmed/25489638>

<http://www.ncbi.nlm.nih.gov/pubmed/27073205>

<http://www.ncbi.nlm.nih.gov/pubmed/29038796>

<http://www.ncbi.nlm.nih.gov/pubmed/30555977>

<http://www.ncbi.nlm.nih.gov/pubmed/30301555>

