Clinical trial results:
A 12-month, Phase 3b, randomized, visual acuity assessor-masked, multicenter study assessing the efficacy and safety of ranibizumab 0.5 mg in treat and extend regimen compared to monthly regimen, in patients with neovascular age-related macular degeneration

Summary

EudraCT number	2013-002626-23
Trial protocol	ES IT BE DE SK GB HU PT DK SI HR
Global end of trial date	19 November 2015

Results information

Result version number	v1 (current)
This version publication date	04 November 2016
First version publication date	04 November 2016

Trial information

Trial identification

Sponsor protocol code	CRFB002A2411

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01948830
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, trialandresults.registries@novartis.com

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	19 November 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that the ranibizumab Treat and Extend regimen (TER) was non-inferior to ranibizumab monthly regimen in patients with nAMD as assessed by the change in best corrected visual acuity (BCVA) from Baseline to Month 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Croatia: 34
Country: Number of subjects enrolled	Denmark: 22
Country: Number of subjects enrolled	Egypt: 10
Country: Number of subjects enrolled	Germany: 68
Country: Number of subjects enrolled	United Kingdom: 40
Country: Number of subjects enrolled	Hungary: 105
Country: Number of subjects enrolled	India: 11
Country: Number of subjects enrolled	Israel: 50
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Portugal: 38
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	Slovakia: 49
Country: Number of subjects enrolled	Slovenia: 2
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	Switzerland: 26
Country: Number of subjects enrolled	Turkey: 12

Worldwide total number of subjects	650
EEA total number of subjects	473

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)	78
From 65 to 84 years	483
85 years and over	89

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were randomized 1:1 into one of two treatment arms, Treat and Extend or monthly regimens.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I ranibizumab 0.5 mg monthly

Arm description:

Ranibizumab 0.5 mg/0.05 mL (Monthly regimen)

Arm type	Active comparator
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	RFB002
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Ranibizumab 0.5 mg/0.05 mL (Monthly regimen)

Arm title	Group II ranibizumab 0.5 mg TER

Arm description:

Ranibizumab 0.5 mg/0.05 mL (TER) treat and Extend regimen

Arm type	Active comparator
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	RFB002
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Ranibizumab 0.5 mg/0.05 mL (TER) treat and Extend regimen

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The blinded roles were verified

Number of subjects in period 1	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER
Started	323	327
Safety Set	323	326
Completed	290	295
Not completed	33	32

Adverse event, serious fatal	3	4
Physician decision	1	3
Consent withdrawn by subject	14	17
Adverse event, non-fatal	9	2
Protocol deviation	1	2
Lost to follow-up	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Group I ranibizumab 0.5 mg monthly
Reporting group description: Ranibizumab 0.5 mg/0.05 mL (Monthly regimen)	
Reporting group title	Group II ranibizumab 0.5 mg TER
Reporting group description: Ranibizumab 0.5 mg/0.05 mL (TER) treat and Extend regimen	

Reporting group values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER	Total
Number of subjects	323	327	650
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	42	36	78
From 65-84 years	234	249	483
85 years and over	47	42	89
Age Continuous Units: Years			
arithmetic mean	75.3	75.2	
standard deviation	± 8.61	± 8.13	-
Gender, Male/Female Units: Subjects			
Female	179	181	360
Male	144	146	290

End points

End points reporting groups

Reporting group title	Group I ranibizumab 0.5 mg monthly
Reporting group description: Ranibizumab 0.5 mg/0.05 mL (Monthly regimen)	
Reporting group title	Group II ranibizumab 0.5 mg TER
Reporting group description: Ranibizumab 0.5 mg/0.05 mL (TER) treat and Extend regimen	

Primary: Change in best corrected visual acuity (BCVA) from Baseline to Month 12

End point title	Change in best corrected visual acuity (BCVA) from Baseline to Month 12
End point description: Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts while participants were in a sitting position at a testing distance of 4 meters. The range of ETDRS is 0 to 100 letters. A positive average change from baseline of BCVA indicates improvement	
End point type	Primary
End point timeframe: Baseline to Month 12	

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	323		
Units: Letters (EDTRS)				
least squares mean (standard error)	6.2 (± 0.7)	8.1 (± 0.7)		

Statistical analyses

Statistical analysis title	Change in BCVA
Comparison groups	Group I ranibizumab 0.5 mg monthly v Group II ranibizumab 0.5 mg TER
Number of subjects included in analysis	643
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANCOVA

Secondary: Number of visits scheduled

End point title	Number of visits scheduled

End point description:

The number of visits scheduled according to the treat and extend regimen after treatment initiation

End point type	Secondary

End point timeframe:

From Month1 to Month 11

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: Number of visits				
arithmetic mean (standard deviation)	8.9 (± 2.56)	11.2 (± 2.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in BCVA from baseline to month 12

End point title	Change in BCVA from baseline to month 12

End point description:

Best Corrected Visual Acuity (BCVA) was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like chart at Baseline and Month 12 while participants were in a sitting position at a testing distance of 4 meters

End point type	Secondary

End point timeframe:

Baseline to Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	323		
Units: Letters (EDTRS)				
arithmetic mean (standard deviation)	6.4 (± 14.11)	8 (± 11.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Average BCVA change from baseline to Month 12

End point title	Average BCVA change from baseline to Month 12

End point description:

Best Corrected Visual Acuity (BCVA) was assessed in a sitting position using ETDRS-like visual acuity testing charts at an initial testing distance of 4 meters. Mean Visual Acuity was averaged over all monthly assessments from Baseline to Month 12

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	320	323		
Units: Letters (EDTRS)				
arithmetic mean (standard deviation)	6.3 (± 10.5)	7.1 (± 9.41)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in visual acuity BCVA (letters) from Baseline to Month 12

End point title	Mean change in visual acuity BCVA (letters) from Baseline to Month 12

End point description:

Best-Corrected Visual Acuity (BCVA) letters was measured using Early Treatment Diabetic Retinopathy Study (ETDRS) -like charts while participants were in a sitting position at a testing distance of 4 meters. The range of ETDRS is 0 to 100 letters. For the mean change of best corrected visual acuity at Month 12 and compare to Baseline

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: Letters (EDTRS)				
arithmetic mean (standard deviation)				
Month 1 (n=320, 322)	4.6 (± 7.56)	4.2 (± 6.98)		
Month 2 (n=240, 316)	5.5 (± 8.64)	5.8 (± 8.58)		
Month 3 (n=247, 311)	6.7 (± 9.09)	6.7 (± 9.19)		
Month 4 (n=213, 314)	7 (± 10.9)	7.3 (± 9.95)		

Month 5 (n=231, 302)	6 (± 11.34)	7.7 (± 10.61)		
month 6 (n=205, 302)	6.9 (± 13.34)	7.9 (± 10.83)		
Month 7 (n=230, 298)	5.9 (± 14.25)	7.9 (± 11.36)		
Month 8 (n=210, 295)	7.5 (± 12.87)	7.9 (± 11.34)		
Month 9 (n=179, 295)	6.6 (± 13.63)	7.6 (± 12.56)		
Month 10 (n=202, 296)	6.3 (± 13.44)	7.6 (± 12.06)		
Month 11 (n=180, 290)	5.9 (± 14.12)	7.5 (± 12.48)		
Month 12 (n=294, 295)	6.6 (± 13.41)	7.9 (± 11.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with a BCVA improvement of ≥1, ≥5, ≥10, ≥15, and ≥30 letters from Baseline to Month 12

End point title	Number of patients with a BCVA improvement of ≥1, ≥5, ≥10, ≥15, and ≥30 letters from Baseline to Month 12

End point description:

BCVA score was based on the number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart assessed at a starting distance of 4 meters. An increased score indicates improvement in acuity. This outcome assessed the number of participants who had improvement of ≥1, ≥5, ≥10, ≥15, and ≥30 letters of visual acuity at Month 12 as compared with baseline

End point type	Secondary

End point timeframe:

Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: Number of participants				
Month 1,Gain of ≥ 1 letter (n=320,322)	235	233		
Month 1, Gain of ≥ 5 letters	145	145		
Month 1, Gain of ≥ 10 letters	65	58		
Month 1, Gain of ≥ 15 letters	24	23		
Month 1, Gain of ≥ 30 letters	4	2		
Month 2, Gain of >= 1 letter (n=226, 316)	168	244		
Month 2, Gain of >= 5 letters	123	184		
Month 2, Gain of >= 10 letters	60	88		
Month 2, Gain of >= 15 letters	30	39		
Month 2, Gain of >= 30 letters	4	3		
Month 3, Gain of >= 1 letter (n=161,311)	120	244		
Month 3, Gain of >= 5 letters	98	187		
Month 3, Gain of >= 10 letters	57	110		

Month 3, Gain of >= 15 letters	28	46		
Month 3, Gain of >= 30 letters	2	3		
Month 4, Gain of >= 1 letter (n=128, 314)	96	249		
Month 4, Gain of >= 5 letters	67	198		
Month 4, Gain of >=10 letters	48	118		
Month 4, Gain of >= 15 letters	25	60		
Month 4, Gain of >= 30 letters	4	8		
Month 5, Gain of >= 1 letter (n=114, 302)	84	243		
Month 5, Gain of >= 5 letters	64	197		
Month 5, Gain of >= 10 letters	42	116		
Month 5, Gain of >= 15 letters	19	59		
Month 5, Gain of >= 30 letters	3	10		
Month 6, Gain of >= 1 letter (n=117, 302)	85	238		
Month 6, Gain of >= 5 letters	68	197		
Month 6, Gain of >= 10 letters	42	125		
Month 6, Gain of >= 15 letters	19	61		
Month 6, Gain of >= 30 letters	2	11		
Month 7, Gain of >= 1 letter (n=176, 298)	126	235		
Month 7, Gain of >= 5 letters	94	196		
Month 7, Gain of >= 10 letters	57	123		
Month 7, Gain of >= 15 letters	33	69		
Month 7, Gain of >= 30 letters	7	9		
Month 8, Gain of >= 1 letter (n=163, 295)	124	228		
Month 8, Gain of >= 5 letters	108	198		
Month 8, Gain of >= 10 letters	69	130		
Month 8, Gain of >= 15 letters	40	72		
Month 8, Gain of >= 30 letters	4	9		
Month 9, Gain of >= 1 letter (n=129, 295)	93	229		
Month 9, Gain of >= 5 letters	78	186		
Month 9, Gain of >= 10 letters	52	128		
Month 9, Gain of >= 15 letters	28	70		
Month 9, Gain of >= 30 letters	5	8		
Month 10, Gain of >= 1 letter (n=159, 296)	113	230		
Month 10, Gain of >= 5 letters	98	190		
Month 10, Gain of >= 10 letters	60	126		
Month 10, Gain of >= 15 letters	32	74		
Month 10, Gain of >= 30 letters	4	10		
Month 11, Gain of >= 1 letter (131, 290)	94	222		
Month 11, Gain of >= 5 letters	79	187		
Month 11, Gain of >= 10 letters	51	130		
Month 11, Gain of >= 15 letters	32	74		
Month 11, Gain of >= 30 letters	5	9		
Month 12, Gain of >= 1 letter (n=291, 295)	217	226		
Month 12, Gain of >= 5 letters	178	199		
Month 12, Gain of >= 10 letters	123	135		
Month 12, Gain of >= 15 letters	75	77		

Month 12, Gain of >= 30 letters	12	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Best Corrected Visual Acuity (BCVA) loss <5, <10, and <15 letters by visit

End point title	Number of patients with Best Corrected Visual Acuity (BCVA) loss <5, <10, and <15 letters by visit

End point description:

Best Corrected Visual Acuity (BCVA) was assessed in a sitting position using ETDRS-like visual acuity testing charts at an initial testing distance of 4 meters.Best Corrected Visual Acuity (BCVA) was assessed in a sitting position using ETDRS-like visual acuity testing charts at an initial testing distance of 4 meters.

End point type	Secondary

End point timeframe:

Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: Number of participants				
Month 1, Loss of < 5 letters (n=320, 322)	296	295		
Month 1, Loss of < 10 letters	313	314		
Month 1, Loss of < 15 letters	319	320		
Month 2, Loss of < 5 letters (n=226, 316)	205	288		
Month 2, Loss of < 10 letters	220	306		
Month 2, Loss of < 15 letters	223	309		
Month 3, Loss of < 5 letters (n=161, 311)	146	289		
Month 3, Loss of < 10 letters	158	299		
Month 3, Loss of < 15 letters	160	304		
Month 4, Loss of < 5 letters (n=128, 314)	114	286		
Month 4, Loss of < 10 letters	128	301		
Month 4, Loss of < 15 letters	124	307		
Month 5, Loss of < 5 letters (n=114, 302)	97	276		
Month 5, Loss of < 10 letters	105	287		
Month 5, Loss of < 15 letters	108	295		
Month 6, Loss of < 5 letters (n=117, 302)	104	271		

Month 6, Loss of < 10 letters	110	286		
Month 6, Loss of < 15 letters	111	298		
Month 7, Loss of < 5 letters (n=176, 298)	148	268		
Month 7, Loss of < 10 letters	162	279		
Month 7, Loss of < 15 letters	166	289		
Month 8, Loss of < 5 letters (n=163, 295)	145	262		
Month 8, Loss of < 10 letters	155	276		
Month 8, Loss of < 15 letters	155	286		
Month 9, Loss of < 5 letters (n=129, 295)	110	258		
Month 9, Loss of < 10 letters	120	270		
Month 9, Loss of < 15 letters	122	281		
Month 10, Loss of < 5 letters(n=159, 296)	133	253		
Month 10, Loss of < 10 letters	147	276		
Month 10, Loss of < 15 letters	150	285		
Month 11, Loss of < 5 letters (n=131, 290)	105	251		
Month 11, Loss of < 10 letters	118	263		
Month 11, Loss of < 15 letters	121	275		
Month 12, Loss of < 5 letters (291, 295)	247	256		
Month 12, Loss of < 10 letters	267	272		
Month 12, Loss of < 15 letters	273	284		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with a BCVA value of ≥ 73 letters (approximate 20/40 Snellen chart equivalent) at Month 12

End point title	Number of patients with a BCVA value of ≥ 73 letters (approximate 20/40 Snellen chart equivalent) at Month 12

End point description:

Best Corrected Visual Acuity (BCVA) was measured using Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts at baseline and month 12 while participants were in a sitting position at a testing distance of 4 meters. The range of EDTRS is 0 to 100 letters. BCVA above 73 letters at Month 12 indicates a positive outcome

End point type	Secondary

End point timeframe:

Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: Number of participants				

Month 1 (n=320, 322)	106	106		
Month 2 (n=226, 316)	74	136		
Month 3 (n=161, 311)	67	148		
Month 4 (n=128, 314)	60	147		
Month 5 (n=114, 302)	51	156		
Month 6 (n=117, 302)	58	155		
Month 7 (n=176, 298)	78	150		
Month 8 (n=163, 295)	84	155		
Month 9 (n=129, 295)	68	156		
Month 10 (n=159, 296)	74	149		
Month 11 (n=131, 290	63	143		
Month 12 (n=291, 295)	131	149		

Statistical analyses

No statistical analyses for this end point

Secondary: The mean number of treatment frequency

End point title	The mean number of treatment frequency
End point description: The number of injections received	
End point type	Secondary
End point timeframe: 12 Months	

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: Number of injections				
arithmetic mean (standard deviation)	8.7 (± 2.68)	11 (± 2.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: The average number of days between injections

End point title	The average number of days between injections
End point description: The average dosing interval was measured as the average number of days between injections	
End point type	Secondary
End point timeframe: Month 12	

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: days				
arithmetic mean (standard deviation)	40.3 (± 11.28)	29.4 (± 3.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with fluid free macula over time up to Month 12

End point title	Percentage of participants with fluid free macula over time up to Month 12

End point description:

OCT (optical coherence tomography) was used to assess intra-retinal fluid as Measured by SD-OCT (Spectral Domain-Optical Coherence Tomography). Fluid free macula refers to absence of macular edema (as assessed by the reading center). The full analysis set was used for this evaluation but the count presented are the counts of patients in the specific treatment group who have a value for the macular edema (center involvement) at study completion. These total counts are used as the denominator for the percentages

End point type	Secondary

End point timeframe:

Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	290		
Units: Percentage of participants				
number (not applicable)				
Absent	60.5	60.7		
Definite	39.5	39		
Can't grade	0	0.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in central subfield retinal thickness (CSFT) over time

End point title	Change in central subfield retinal thickness (CSFT) over time

End point description:

OCT (optical coherence tomography) was used to assess CSFT (Central Sub-Field Thickness) representing the average retinal thickness of the circular area within 1 mm diameter around the foveal center. The Ns in the rows is the number of patients with a value for both baseline and the specific post-baseline visit

End point type	Secondary

End point timeframe:

Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	327		
Units: microns				
arithmetic mean (standard deviation)				
Month 1 (n=311, 316)	-137.6 (± 132.33)	-126.8 (± 119.47)		
Month 2 (n=220, 311)	-151.6 (± 151.15)	-149.2 (± 137.6)		
Month 3 (n=157, 304)	-149.8 (± 167.26)	-151.8 (± 149.51)		
Month 4 (n=125, 307)	-141.8 (± 183.71)	-161.3 (± 149.36)		
Month 5 (n=110, 295)	-138.6 (± 160.04)	-160.9 (± 148.23)		
Month 6 (n=113, 298)	-140.1 (± 156.25)	-163.4 (± 157.18)		
Month 7 (n=173, 296)	-146.6 (± 160.72)	-166.9 (± 161.49)		
Month 8 (n=159, 290)	-153.4 (± 151.93)	-170.4 (± 156.68)		
Month 9 (n=126, 286)	-150.2 (± 153.82)	-169.3 (± 156.5)		
Month 10 (n=156, 291)	-154.6 (± 162.77)	-170.9 (± 153.9)		
Month 11 (n=127, 285)	-133.1 (± 170.47)	-174.8 (± 163.16)		
Month 12 (n=289, 287)	-172.1 (± 162.81)	-173.3 (± 154.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with Choroidal Neovascularization (CNV) leakage assessed by fluorescein angiography (FA) in the study eye at

End point title	Percentage of patients with Choroidal Neovascularization (CNV) leakage assessed by fluorescein angiography (FA) in the study

	eye at

End point description:

To evaluate presence of active CNV leakage on fluorescein angiography (FA) by reading center over time up to Month 12. The full analysis set was used for this evaluation but the count presented are the counts of patients in the specific treatment group who have a value for the presence of leakage at study completion. These total counts are used as the denominator for the percentages.

End point type	Secondary

End point timeframe:

Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	278	286		
Units: Percentage of participants				
number (not applicable)				
Yes	18.7	17.1		
No	74.1	76.9		
Can't grade	0	2.4		
Not applicable	7.2	3.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in composite score of the National Eye Institute-Visual Function Questionnaire-25 (NEI-VFQ-25)

End point title	Change from Baseline in composite score of the National Eye Institute-Visual Function Questionnaire-25 (NEI-VFQ-25)

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicates the best possible response. The composite score and score of each of each construct also ranged from 0 to 100 as they are calculated as total scores divided by the number of questions. The higher the values of total scores represent better outcome

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Group I ranibizumab 0.5 mg monthly	Group II ranibizumab 0.5 mg TER		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	290	293		
Units: Score on a scale				
arithmetic mean (standard deviation)	2.3 (± 13.93)	4 (± 13.72)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Ranibizumab 0.5 mg Treat and Extend

Reporting group description:

Ranibizumab 0.5 mg Treat and Extend

Reporting group title	Ranibizumab 0.5 mg Monthly

Reporting group description:

Ranibizumab 0.5 mg Monthly

Serious adverse events	Ranibizumab 0.5 mg Treat and Extend	Ranibizumab 0.5 mg Monthly	
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 323 (12.07%)	42 / 326 (12.88%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			

subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 323 (0.00%)	2 / 326 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer metastatic			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid neoplasm			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 323 (0.31%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 323 (0.62%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 323 (0.62%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	2 / 323 (0.62%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood pressure decreased			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intraocular pressure increased (Fellow eye)			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased (Study eye)			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			

subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 323 (0.62%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 323 (0.31%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle rupture			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			

subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 323 (0.31%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	2 / 323 (0.62%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Palpitations			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery thrombosis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 323 (0.00%)	2 / 326 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			

subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 323 (0.00%)	2 / 326 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 323 (0.31%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	3 / 323 (0.93%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paresis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 323 (0.62%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			

subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract (Fellow eye)			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal erosion (Study eye)			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal infiltrates (Study eye)			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryostenosis acquired (Fellow eye)			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dacryostenosis acquired (Study eye)			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole (Study eye)			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment (Study eye)			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage (Study eye)			

subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear (Study eye)			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage (Study eye)			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 323 (0.31%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder prolapse			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 323 (0.31%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			

subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 323 (0.62%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 323 (0.31%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis (Fellow eye)			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endophthalmitis (Study eye)			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 323 (1.24%)	2 / 326 (0.61%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 323 (0.00%)	1 / 326 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercreatininaemia			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 323 (0.31%)	0 / 326 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Ranibizumab 0.5 mg Treat and Extend	Ranibizumab 0.5 mg Monthly	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	133 / 323 (41.18%)	141 / 326 (43.25%)	
Investigations			
Intraocular pressure increased (Fellow eye)			
subjects affected / exposed	3 / 323 (0.93%)	8 / 326 (2.45%)	
occurrences (all)	3	13	
Intraocular pressure increased (Study eye)			
subjects affected / exposed	27 / 323 (8.36%)	28 / 326 (8.59%)	
occurrences (all)	48	63	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 323 (7.12%)	13 / 326 (3.99%)	
occurrences (all)	24	14	
Eye disorders			
Age-related macular degeneration (Fellow eye)			
subjects affected / exposed	9 / 323 (2.79%)	4 / 326 (1.23%)	
occurrences (all)	9	4	
Blepharitis (Fellow eye)			
subjects affected / exposed	6 / 323 (1.86%)	8 / 326 (2.45%)	
occurrences (all)	6	10	
Cataract (Fellow eye)			
subjects affected / exposed	7 / 323 (2.17%)	10 / 326 (3.07%)	
occurrences (all)	7	10	
Cataract (Study eye)			
subjects affected / exposed	7 / 323 (2.17%)	7 / 326 (2.15%)	
occurrences (all)	7	8	
Choroidal neovascularisation (Fellow eye)			
subjects affected / exposed	6 / 323 (1.86%)	7 / 326 (2.15%)	
occurrences (all)	7	7	
Conjunctival haemorrhage (Study eye)			
subjects affected / exposed	14 / 323 (4.33%)	19 / 326 (5.83%)	
occurrences (all)	15	23	
Dry eye (Fellow eye)			

subjects affected / exposed	7 / 323 (2.17%)	6 / 326 (1.84%)	
occurrences (all)	7	6	
Dry eye (Study eye)			
subjects affected / exposed	6 / 323 (1.86%)	7 / 326 (2.15%)	
occurrences (all)	6	7	
Eye pain (Study eye)			
subjects affected / exposed	10 / 323 (3.10%)	5 / 326 (1.53%)	
occurrences (all)	11	7	
Neovascular age-related macular degeneration (Fellow eye)			
subjects affected / exposed	8 / 323 (2.48%)	16 / 326 (4.91%)	
occurrences (all)	8	20	
Retinal haemorrhage (Study eye)			
subjects affected / exposed	5 / 323 (1.55%)	8 / 326 (2.45%)	
occurrences (all)	5	8	
Visual acuity reduced (Study eye)			
subjects affected / exposed	15 / 323 (4.64%)	12 / 326 (3.68%)	
occurrences (all)	16	15	
Infections and infestations			
Bronchitis			
subjects affected / exposed	6 / 323 (1.86%)	12 / 326 (3.68%)	
occurrences (all)	8	12	
Conjunctivitis (Study eye)			
subjects affected / exposed	10 / 323 (3.10%)	6 / 326 (1.84%)	
occurrences (all)	10	6	
Influenza			
subjects affected / exposed	9 / 323 (2.79%)	12 / 326 (3.68%)	
occurrences (all)	9	13	
Nasopharyngitis			
subjects affected / exposed	18 / 323 (5.57%)	26 / 326 (7.98%)	
occurrences (all)	19	32	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2015	Clarification for the specific timing of the study completion visit in the Treat and Extend regimen (TER) was added. Clarification on the timing of SAE reporting for patients has been added. Minor editorial clarifications were added as well.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported