Clinical trial results:
A 12-month, randomized, double-masked, sham-controlled, multicenter study to evaluate the efficacy and safety of 0.5mg ranibizumab intravtitreal injections in patients with visual impairment due to vascular endothelial growth factor (VEGF) driven macular edema

Summary

EudraCT number	2012-005418-20
Trial protocol	SK IT GB LV HU CZ IE ES BE NL DE FR
Global end of trial date	09 September 2015

Results information

Result version number	v1 (current)
This version publication date	25 June 2016
First version publication date	25 June 2016

Trial information

Trial identification

Sponsor protocol code	CRFB002G2302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01846299
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 x,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111 x,

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	09 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that an individualized regimen of intravitreal injection of 0.5 mg ranibizumab has superior efficacy compared to sham treatment in adult patients with visual impairment due to ME. The primary objective was assessed by the best-corrected visual acuity (BCVA) change from baseline to Month 2.

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. 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	10 October 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	Australia: 15
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	United Kingdom: 26
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Israel: 22
Country: Number of subjects enrolled	Italy: 15
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Latvia: 12
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Russian Federation: 5
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Switzerland: 6

Country: Number of subjects enrolled	Turkey: 7
Worldwide total number of subjects	178
EEA total number of subjects	107

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)	89
From 65 to 84 years	81
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 181 participants were enrolled. Of these, 178 adults were randomized in a 2:1 ratio and considered for analysis. Additionally, the study included 3 adolescent participants, non-randomized, who received open-label treatment and were not included in the analyses.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ranibizumab

Arm description:

A 0.5 mg ranibizumab intravitreal injection was given to the study eye at baseline, and then as needed based on evidence of disease activity.

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

Dosage and administration details:

0.5 mg ranibizumab intravitreal injection to the study eye at baseline, and then as needed based on evidence of disease activity

Arm title	Sham

Arm description:

Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis.

Arm type	Placebo
Investigational medicinal product name	Sham
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis. The sham vial did not contain active drug (empty sterile vial). The sham injection was an imitation of an intravitreal injection using an injection syringe without a needle touching the eye.

Number of subjects in period 1	Ranibizumab	Sham
Started	118	60
Completed	106	50
Not completed	12	10
Adverse event, serious fatal	1	2
Physician decision	4	2
Consent withdrawn by subject	1	6
Adverse event, non-fatal	2	-
Protocol deviation	1	-
Lost to follow-up	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Ranibizumab
Reporting group description:	
A 0.5 mg ranibizumab intravitreal injection was given to the study eye at baseline, and then as needed based on evidence of disease activity.	
Reporting group title	Sham
Reporting group description:	
Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis.	

Reporting group values	Ranibizumab	Sham	Total
Number of subjects	118	60	178
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)	52	37	89
From 65-84 years	62	19	81
85 years and over	4	4	8
Age Continuous |			
Units: Years			
arithmetic mean	63.5	61.8	
standard deviation	± 13.97	± 15.55	-
Gender, Male/Female			
Units: Participants			
Female	45	23	68
Male	73	37	110

End points

End points reporting groups

Reporting group title	Ranibizumab

Reporting group description:

A 0.5 mg ranibizumab intravitreal injection was given to the study eye at baseline, and then as needed based on evidence of disease activity.

Reporting group title	Sham

Reporting group description:

Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis.

Subject analysis set title	Sham with ranibizumab
Subject analysis set type	Full analysis

Subject analysis set description:

Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis.

Subject analysis set title	Sham with ranibizumab
Subject analysis set type	Full analysis

Subject analysis set description:

Sham injection was given to the study eye at baseline, and then treatment was given based on evidence of disease activity. At Month 1, if treatment was needed, sham was administered. At Month 2, participants could switch to open-label ranibizumab on an as needed basis.

Subject analysis set title	Sham without ranibizumab
Subject analysis set type	Full analysis

Subject analysis set description:

Participants did not receive ranibizumab at any time during the study.

Subject analysis set title	Sham without Ranibizumab
Subject analysis set type	Full analysis

Subject analysis set description:

Participants did not receive ranibizumab at any time during the study.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set

Primary: Change from baseline in best-corrected visual acuity (BCVA) in study eye

End point title	Change from baseline in best-corrected visual acuity (BCVA) in study eye[1]

End point description:

BCVA was assessed in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity (VA) testing charts at an initial testing distance of 4 meters. A positive change from baseline indicated improvement.

End point type	Primary

End point timeframe:

Baseline, Month 2

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: letters				
least squares mean (standard error)	5.7 (± 0.81)	2.9 (± 0.89)		

Statistical analyses

Statistical analysis title	Change from baseline in BCVA in the study eye
Comparison groups	Ranibizumab v Sham with ranibizumab
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0111
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	5.16
Variability estimate	Standard error of the mean
Dispersion value	1.203

Secondary: Change from baseline in BCVA in study eye up to Month 2

End point title	Change from baseline in BCVA in study eye up to Month 2[2]

End point description:

BCVA was assessed in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity (VA) testing charts at an initial testing distance of 4 meters. A positive change from baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline, Month 1, Month 2

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: letters				
least squares mean (standard error)				
Month 1 (n=116,59)	4.7 (± 0.7)	1.4 (± 0.98)		
Month 2 (n=114,59)	5.8 (± 0.76)	2.8 (± 1.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in central subfield thickness (CSFT) in study eye

End point title	Change from baseline in central subfield thickness (CSFT) in study eye[3]

End point description:

CSFT wasassessed by optical coherence tomography (OCT). A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: micrometers (um)				
arithmetic mean (standard deviation)				
Month 1 (n=112,59)	-83.6 (± 127.45)	-14.3 (± 97.36)		
Month 2 (n=112,59)	-82.5 (± 140.06)	-30.6 (± 102.77)		
Month 3 (n=113,59)	-86.5 (± 136.43)	-92.2 (± 129.85)		
Month 4 (n=109,57)	-94.5 (± 141.55)	-95.5 (± 140.68)		
Month 5 (n=105,57)	-98.6 (± 136.28)	-107.6 (± 142.22)		
Month 6 (n=109,54)	-110.6 (± 133.1)	-84.1 (± 137.86)		
Month 7 (n=105,52)	-113.3 (± 130.84)	-112.9 (± 148.13)		
Month 8 (n=105,51)	-113.1 (± 127.11)	-107.7 (± 157.4)		
Month 9 (n=105,52)	-111.6 (± 127.99)	-116.3 (± 146.43)		
Month 10 (n=103,50)	-114.1 (± 131.12)	-116.6 (± 147.26)		
Month 11 (n=101,49)	-112.1 (± 124)	-123.5 (± 140.65)		
Month 12 (n=103,50)	-121 (± 124.67)	-116.8 (± 137.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in central subfield volume (CSFV) in study eye

End point title	Change from baseline in central subfield volume (CSFV) in study eye[4]

End point description:

CSFV was assessed OCT. A negative change from baseline indicates improvement.

End point type	Secondary

End point timeframe:

Months 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: microliters (ul)				
arithmetic mean (standard deviation)				
Month 1 (n=112,59)	-0.296 (± 0.457)	-0.032 (± 0.3969)		
Month 2 (n=112,59)	-0.276 (± 0.5362)	-0.104 (± 0.3958)		
Month 3 (n=113,59)	-0.322 (± 0.5812)	-0.348 (± 0.5075)		
Month 4 (n=109,57)	-0.333 (± 0.5568)	-0.378 (± 0.5436)		
Month 5 (n=105,57)	-0.383 (± 0.5592)	-0.401 (± 0.5893)		
Month 6 (n=109,54)	-0.388 (± 0.5167)	-0.344 (± 0.553)		
Month 7 (n=105,52)	-0.438 (± 0.5267)	-0.438 (± 0.6098)		
Month 8 (n=105,51)	-0.405 (± 0.5074)	-0.421 (± 0.6484)		
Month 9 (n=105,52)	-0.446 (± 0.6066)	-0.444 (± 0.621)		
Month 10 (n=103,50)	-0.439 (± 0.6241)	-0.433 (± 0.6407)		
Month 11 (n=101,49)	-0.406 (± 0.4871)	-0.459 (± 0.6157)		
Month 12 (n=103,50)	-0.447 (± 0.4837)	-0.455 (± 0.591)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with presence or absence of intra-retinal fluid in study eye compared to baseline

End point title	Number of participants with presence or absence of intra-retinal fluid in study eye compared to baseline[5]

End point description:

The presence of intra-retinal fluid was assessed by OCT.

End point type	Secondary

End point timeframe:

Month 2, Month 6, Month 12

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: Participants				
Month 2, Absent (n=112,59)	98	46		
Month 2, Definite (n=112,59)	14	13		
Month 6, Absent (n=109,55)	97	43		
Month 6, Definite (n=109,55)	12	12		
Month 12, Absent (n=103,50)	78	39		
Month 12, Definite (n=103,50)	25	11		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with presence or absence of subretinal fluid in study eye compared to baseline

End point title	Number of participants with presence or absence of subretinal fluid in study eye compared to baseline[6]

End point description:

The presence of subretinal fluid was assessed by OCT.

End point type	Secondary

End point timeframe:

Month 2, Month 6, Month 12

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: Participants				
Month 2, Absent (n=113,59)	77	33		
Month 2, Definite (n=110,55)	36	26		
Month 6, Absent (n=109,55)	75	35		
Month 6, Definite (n=109,55)	35	20		
Month 12, Absent (n=104,50)	77	37		
Month 12, Definite (n=103,50)	27	13		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with presence of active macular edema (ME) leakage

End point title	Number of participants with presence of active macular edema (ME) leakage[7]

End point description:

The presence of active ME leakage was assessed by fluorescein angiography (FA).

End point type	Secondary

End point timeframe:

Month 2

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: Participants	96	53		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants requiring rescue treatment at Month 1

End point title	Number of participants requiring rescue treatment at Month 1[8]

End point description:

Rescue treatment with laser photocoagulation or periocular treatment could be administered at Month 1 only if the participant had a visual acuity loss of > 5 letters due to disease activity from baseline to Month 1.

End point type	Secondary

End point timeframe:

Month 1

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Average change from baseline in BCVA

End point title	Average change from baseline in BCVA[9]

End point description:

BCVA was assessed in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity (VA) testing charts at an initial testing distance of 4 meters. A positive change from baseline indicated improvement.

End point type	Secondary

End point timeframe:

Baseline (BL), month 1 through month 6, month 1 through month 12

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: letters				
arithmetic mean (standard deviation)				
Average change from BL, month 1 through month 6	6.39 (± 8.405)	4.5 (± 8.095)		
Average change from BL, month 1 through month 12	7.4 (± 9.052)	5.82 (± 8.927)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with ≥ 1, ≥ 5, ≥ 10 and ≥ 15 letters gain or reaching 84 letters

End point title	Proportion of patients with ≥ 1, ≥ 5, ≥ 10 and ≥ 15 letters gain or reaching 84 letters[10]

End point description:

VA measurements (number of letters correctly identified) were performed with the patient in a sitting position using ETDRS-like visual acuity testing charts at a testing distance of 4 meters.

End point type	Secondary

End point timeframe:

Month 2, Month 6 , Month 12

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: Participants				
Month 2, Gain of >= 15 letters (n=114,59)	26	7		
Month 2, Gain of >= 10 letters (n=114,59)	35	11		
Month 2, Gain of >= 5 letters (n=114,59)	55	19		
Month 2, Gain of >= 1 letter (n=114,59)	80	38		
Month 6, Gain of >= 15 letters (n=111,55)	30	15		
Month 6, Gain of >= 10 letters (n=111,55)	41	21		
Month 6, Gain of >= 5 letters (n=111,55)	67	34		
Month 6, Gain of >= 1 letters (n=111,55)	87	40		
Month 12, Gain of >= 15 letters (n=106,50)	44	22		
Month 12, Gain of >= 10 letters (n=106,50)	55	27		
Month 12, Gain of >= 5 letters (n=106,50)	72	37		
Month 12, Gain of >= 1 letters (n=106,50)	86	42		

Statistical analyses

No statistical analyses for this end point

Secondary: Porportion of patients with > 1, > 5, > 10 and > 15 letters loss

End point title	Porportion of patients with > 1, > 5, > 10 and > 15 letters

End point description:

VA measurements (number of letters correctly identified) were performed with the patient in a sitting position using ETDRS-like visual acuity testing charts at a testing distance of 4 meters.

End point type	Secondary

End point timeframe:

Month 2, Month 6, Month 12

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	117	60		
Units: Participants				
Month 2, Loss of >1 letter (n=114,59)	17	9		
Month 2, Loss of >5 letters (n=114,59)	8	4		
Month 2, Loss of >10 letters (n=114,59)	2	3		
Month 2, Loss of >15 letters (n=114,59)	0	0		
Month 6, Loss of >1 letter (n=111,55)	14	12		
Month 6, Loss of >5 letters (n=111,55)	5	7		
Month 6, Loss of >10 letters (n=111,55)	3	4		
Month 6, Loss of >15 letters (n=111,55)	1	1		
Month 12, Loss of >= 1 letter (n=106,50)	10	5		
Month 12, Loss of >= 5 letters (n=106,50)	6	3		
Month 12, Loss of >= 10 letters (n=106,50)	2	3		
Month 12, Loss of >= 15 letters (n=106,50)	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with ranibizumab treatments

End point title	Number of participants with ranibizumab treatments[12]

End point description:

The number of participants administered study treatments, according to treatment frequency, was assessed.

End point type	Secondary

End point timeframe:

Month 12

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab	Sham without ranibizumab	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	118	56	2	
Units: Participants				
Frequency of injections = 0	0	0	2	
Frequency of injections = 1	13	6	0	
Frequency of injections = 2	5	3	0	
Frequency of injections = 3	14	7	0	
Frequency of injections = 4	3	5	0	
Frequency of injections = 5	17	7	0	
Frequency of injections = 6	7	11	0	
Frequency of injections = 7	6	0	0	
Frequency of injections = 8	13	0	0	
Frequency of injections = 9	3	6	0	
Frequency of injections = 10	12	11	0	
Frequency of injections = 11	6	0	0	
Frequency of injections = 12	20	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with re-treatments

End point title	Number of participants with re-treatments[13]

End point description:

The number of participants, administered re-treatments according to treatment frequency, was assessed. Re-treatment was defined as an administration of study medication following at least one non-missed visit where treatment was not administered in the study eye. Up to Month 12, the maximum number of retreatments was 5.

End point type	Secondary

End point timeframe:

Month 6, Month 12

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab	Sham without ranibizumab	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	118	56	2	
Units: Participants				
Month 6, Frequency of re-treatment = 1	34	15	0	
Month 6, Frequency of re-treatment = 2	15	3	0	
Month 12, Frequency of re-treatment = 1	21	12	0	

Month 12, Frequency of re-treatment = 2	24	7	0	
Month 12, Frequency of re-treatment = 3	13	5	0	
Month 12, Frequency of re-treatment = 4	5	5	0	
Month 12, Frequency of re-treatment = 5	3	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of primary reasons for decision to treat by Investigator

End point title	Number of primary reasons for decision to treat by

End point description:

The total number of primary reasons for decisions to treat was assessed. A single participant could have had multiple primary reasons for treatment.

End point type	Secondary

End point timeframe:

12 months

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: All arms do not apply to the end point.

End point values	Ranibizumab	Sham with ranibizumab	Sham without Ranibizumab	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	118	56	2	
Units: Participants				
Vision impairment	38	22	0	
OCT abnormality	637	345	1	
FA abnormality	11	5	0	
Color fundus photography abnormality	0	0	0	
Clinical abnormality	3	0	0	
Without documentation (missing reason)	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from 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	18.0

Reporting groups

Reporting group title	Ranibizumab 0.5 mg
Reporting group description:	
Ranibizumab 0.5 mg	
Reporting group title	Sham with Ranibizumab 0.5 mg
Reporting group description:	
Sham with Ranibizumab 0.5 mg	
Reporting group title	Sham without Ranibizumab 0.5 mg
Reporting group description:	
Sham without Ranibizumab 0.5 mg	

Serious adverse events	Ranibizumab 0.5 mg	Sham with Ranibizumab 0.5 mg	Sham without Ranibizumab 0.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 119 (12.61%)	6 / 56 (10.71%)	1 / 2 (50.00%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular carcinoma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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
Malignant melanoma			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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

Meningioma benign			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 119 (1.68%)	0 / 56 (0.00%)	0 / 2 (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
Investigations			

Prostatic specific antigen increased			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Shunt stenosis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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
Nervous system disorders			
Basilar artery thrombosis			
subjects affected / exposed	0 / 119 (0.00%)	0 / 56 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem stroke			
subjects affected / exposed	0 / 119 (0.00%)	0 / 56 (0.00%)	1 / 2 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral haemorrhage			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Dizziness			

subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Presyncope			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Eye disorders			
Conjunctivitis allergic (Fellow treated eye)			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Conjunctivitis allergic (Study eye)			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Corneal oedema (Fellow treated eye)			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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
Open angle glaucoma (Fellow untreated eye)			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Open angle glaucoma (Study eye)			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Gastrointestinal disorders			

Gastritis			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Pancreatitis acute			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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			
Biliary colic			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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 and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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
Nephrolithiasis			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Urinary tract obstruction			

subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Musculoskeletal and connective tissue disorders			
Mobility decreased			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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
Muscular weakness			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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
Infections and infestations			
Endophthalmitis (Study eye)			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Herpes zoster cutaneous disseminated			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 119 (0.84%)	0 / 56 (0.00%)	0 / 2 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 119 (0.00%)	1 / 56 (1.79%)	0 / 2 (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

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

Non-serious adverse events	Ranibizumab 0.5 mg	Sham with Ranibizumab 0.5 mg	Sham without Ranibizumab 0.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 119 (48.74%)	21 / 56 (37.50%)	0 / 2 (0.00%)
Investigations			
Intraocular pressure increased (Study eye)			
subjects affected / exposed	6 / 119 (5.04%)	3 / 56 (5.36%)	0 / 2 (0.00%)
occurrences (all)	9	6	0
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 119 (5.04%)	2 / 56 (3.57%)	0 / 2 (0.00%)
occurrences (all)	7	3	0
Eye disorders			
Conjunctival haemorrhage (Study eye)			
subjects affected / exposed	11 / 119 (9.24%)	7 / 56 (12.50%)	0 / 2 (0.00%)
occurrences (all)	16	10	0
Cystoid macular oedema (Study eye)			
subjects affected / exposed	6 / 119 (5.04%)	0 / 56 (0.00%)	0 / 2 (0.00%)
occurrences (all)	7	0	0
Dry eye (Study eye)			
subjects affected / exposed	6 / 119 (5.04%)	1 / 56 (1.79%)	0 / 2 (0.00%)
occurrences (all)	6	1	0
Eye pain (Study eye)			
subjects affected / exposed	10 / 119 (8.40%)	2 / 56 (3.57%)	0 / 2 (0.00%)
occurrences (all)	11	2	0
Macular oedema (Fellow untreated eye)			
subjects affected / exposed	1 / 119 (0.84%)	3 / 56 (5.36%)	0 / 2 (0.00%)
occurrences (all)	1	3	0
Macular oedema (Study eye)			
subjects affected / exposed	7 / 119 (5.88%)	2 / 56 (3.57%)	0 / 2 (0.00%)
occurrences (all)	8	5	0
Visual acuity reduced (Study eye)			
subjects affected / exposed	11 / 119 (9.24%)	3 / 56 (5.36%)	0 / 2 (0.00%)
occurrences (all)	15	3	0
Infections and infestations			

Influenza			
subjects affected / exposed	6 / 119 (5.04%)	3 / 56 (5.36%)	0 / 2 (0.00%)
occurrences (all)	9	4	0
Nasopharyngitis			
subjects affected / exposed	12 / 119 (10.08%)	2 / 56 (3.57%)	0 / 2 (0.00%)
occurrences (all)	15	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2014	The alignment of the protocol-specified retreatment criteria with current medical practice for the management of patients with visual impairment due to ME, specifically the inclusion of anatomical parameters in addition to BCVA. The optional test, electroretinography (ERG), was removed based on expert feedback. The eligibility criteria for patients with rare diseases were clarified to improve the quality of the patient population by 1) excluding patients with diseases and conditions that were known to spontaneously resolve and/or those in which the use of VEGF inhibitors is controversial and 2) allowed the inclusion of patients with other diseases and conditions that could potentially benefit from treatment with ranibizumab.
31 March 2015	Error was corrected in Section on Prior and concomitant treatment from "During the study, the use of topical corticosteroids and NSAIDs in the study eye to treat an active ocular condition other than the CNV is permitted" to "…other than the ME is permitted". Section on risks and benefits was updated. Several typo corrections together with an administrative update were implemented.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported