Clinical trial results:
A 12-month, open-label, interventional, multicentre study to investigate the current criteria driving re-treatment with ranibizumab upon relapse in patients with visual impairment due to choroidal neovascularization secondary to pathologic myopia

Summary

EudraCT number	2013-003334-33
Trial protocol	IT
Global end of trial date	15 July 2016

Results information

Result version number	v1 (current)
This version publication date	27 July 2017
First version publication date	27 July 2017

Trial information

Trial identification

Sponsor protocol code	CRFB002FIT01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02034006
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,

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	15 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 July 2016
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 investigate current criteria driving retreatment in patients affected by CNV secondary to PM and experiencing a relapse of the disease after the first administration of ranibizumab. The criteria for retreatment may have consisted in patient subjectivity or in clinical findings following examination (BCVA, fundus), and/or optical coherence tomography (OCT), and/or fluorescein angiography (FAG).

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. The investigator could prescribe any medication and/or supportive care during the study based on clinical needs.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2014
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	Italy: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	114

From 65 to 84 years	85
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Two hundred fifteen (215) subjects were screened in this study (i.e. provided written informed consent). Two hundred (200) subjects underwent baseline visit and received at least one injection of ranibizumab.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ranibizumab

Arm description:

Patients treated with a single ranibizumab 0.5 mg/0.05ml intravitreal injection. Further injections might be required when monitoring reveals disease activity.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	RFB002
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Ocular use

Dosage and administration details:

All patients received a single initial intravitreal injection of ranibizumab 0.5 mg/0.05 ml as per Committee for Human Medicinal Products (CHMP)approval. Further injections might have been required when monitoring reveals disease activity. Disease activity, defined as reduced visual acuity and/or signs of lesion activity, was evaluated based on clinical examination (BCVA, fundus), and/or optical coherence tomography (OCT), and/or fluorescein angiography (FAG). Bilateral treatment was allowed provided at least 14 days of intercurrence.

Number of subjects in period 1	Ranibizumab
Started	200
Once Treated Patients	70 [1]
Re-treated patients	130 [2]
Completed	186
Not completed	14
Adverse event, serious fatal	1
Consent withdrawn by subject	7
Pregnancy	1
Lost to follow-up	5

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Out of total patients who took at least one ranibizumab injection, these patients received more than once.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Out of total patients who took at least one ranibizumab injection, these patients only received once.

Baseline characteristics

Reporting groups	
Reporting group title	Ranibizumab
Reporting group description:	
Patients treated with a single ranibizumab 0.5 mg/0.05ml intravitreal injection. Further injections might be required when monitoring reveals disease activity.	

Reporting group values	Ranibizumab	Total	
Number of subjects	200	200	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age Continuous Units: Years			
arithmetic mean	61.82		
standard deviation	± 12.67	-	
Gender, Male/Female Units: Subjects			
Female	53	53	
Male	147	147	

End points

End points reporting groups

Reporting group title	Ranibizumab
Reporting group description:	
Patients treated with a single ranibizumab 0.5 mg/0.05ml intravitreal injection. Further injections might be required when monitoring reveals disease activity.	
Subject analysis set title	Ranibizumab: Treated Once
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients treated only once with a single ranibizumab 0.5 mg/0.05ml intravitreal injection.	
Subject analysis set title	Ranibizumab: Re-treated Once
Subject analysis set type	Full analysis
Subject analysis set description:	
Patients treated more than once with a single ranibizumab 0.5 mg/0.05ml intravitreal injection.	

Primary: Number of patients treated and re-treated based on presence/absence of active leakage

End point title	Number of patients treated and re-treated based on presence/absence of active leakage
End point description:	
Presence of active leakage on fluorescein angiography (FAG) was assessed at screening (14 to 3 days before baseline visit), month 2 and month 6. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of presence of active leakage (Yes/No). For retreated patients, the presence/absence of active leakage was considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis. Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients undergoing Fluorescein angiography during that time point.	
End point type	Primary
End point timeframe:	
Screening, Month 2, Month 6	

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Screening: Active leakage, No (n= 64, 124)	3	0		
Screening: Active leakage, Yes (n= 64, 124)	61	121		
Screening: Active leakage, NE (n= 64, 124)	0	2		
Screening: Active leakage, Missing (n= 64, 124)	0	1		
Month 2: Active leakage, No (n= 61, 119)	58	61		
Month 2: Active leakage, Yes (n= 61, 119)	3	56		

Month 2: Active leakage, NE (n= 61, 119)	0	2		
Month 6: Active leakage, No (n= 60, 115)	55	73		
Month 6: Active leakage, Yes (n= 60, 115)	4	40		
Month 6: Active leakage, NE (n= 60, 115)	1	2		

Statistical analyses

Statistical analysis title	Presence vs. absence of active leakage
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	72.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.44
upper limit	223.42

Primary: Number of patients treated and re-treated based on presence/absence of macular edema

End point title	Number of patients treated and re-treated based on presence/absence of macular edema

End point description:

Presence of macular edema from optical coherence tomography (OCT) was assessed at screening (14 to 3 days before baseline visit), month 2, month 6 and month 12. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of presence of macular edema (Yes/No). For retreated patients, the presence/absence of macular edema was considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis. *NE = Not evaluable. Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients undergoing OCT during that time point.

End point type	Primary

End point timeframe:

Screening, Month 2, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Screening: Macular Edema, No (n= 69, 129)	38	63		
Screening: Macular Edema, Yes (n= 69, 129)	28	65		
Screening: Macular Edema, NE (n= 69, 129)	3	1		
Month 2: Macular Edema, No (n= 63, 129)	59	103		
Month 2: Macular Edema, Yes (n= 63, 129)	3	24		
Month 2: Macular Edema, NE (n= 63, 129)	1	2		
Month 6: Macular Edema, No (n= 60, 126)	57	101		
Month 6: Macular Edema, Yes (n= 60, 126)	2	24		
Month 6: Macular Edema, NE(n= 60, 126)	1	1		
Month 12: Macular Edema, No (n= 61, 124)	56	108		
Month 12: Macular Edema, Yes (n= 61, 124)	4	15		
Month 12: Macular Edema, NE (n= 61, 124)	1	1		

Statistical analyses

Statistical analysis title	Presence vs. absence of macular edema
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.18
upper limit	27.36

Primary: Number of patients treated and re-treated based on presence/absence of cysts

End point title	Number of patients treated and re-treated based on presence/absence of cysts

End point description:

Presence of cysts from optical coherence tomography (OCT) was assessed at screening (14 to 3 days before baseline visit), month 2, month 6 and month 12. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of presence of cysts (Yes/No). For retreated patients, the presence/absence of cysts was considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis. *NE = Not evaluable
Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients undergoing OCT during that time point.

End point type	Primary

End point timeframe:

Screening, Month 2, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Screening: Cysts, No (n= 69, 129)	41	79		
Screening: Cysts, Yes (n= 69, 129)	27	50		
Screening: Cysts, NE (n= 69, 129)	1	0		
Month 2: Cysts, No (n= 63, 129)	60	94		
Month 2: Cysts, Yes (n= 63, 129)	2	32		
Month 2: Cysts, NE (n= 63, 129)	1	2		
Month 2: Cysts, Missing (n= 63, 129)	0	1		
Month 6: Cysts, No (n= 60, 126)	57	98		
Month 6: Cysts, Yes (n= 60, 126)	2	27		
Month 6: Cysts, NE(n= 60, 126)	1	1		
Month 12: Cysts, No (n= 61, 124)	57	97		
Month 12: Cysts, Yes (n= 61, 124)	3	26		
Month 12: Cysts, NE (n= 61, 124)	1	1		

Statistical analyses

Statistical analysis title	Presence vs. absence of cysts
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.76
upper limit	42.67

Primary: Number of patients treated and re-treated based on presence/absence of Intra-retinal fluid

End point title	Number of patients treated and re-treated based on presence/absence of Intra-retinal fluid

End point description:

Presence of Intra-retinal fluid from optical coherence tomography (OCT) was assessed at screening (14 to 3 days before baseline visit), month 2, month 6 and month 12. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of presence of Intra-retinal fluid (Yes/No). For retreated patients, the presence/absence of Intra-retinal fluid was considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis. *NE = Not evaluable

Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients undergoing OCT during that time point.

End point type	Primary

End point timeframe:

Screening, Month 2, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Screening: Intra-retinal fluid, No (n= 69, 129)	19	37		
Screening: Intra-retinal fluid, Yes (n= 69, 129)	49	90		
Screening: Intra-retinal fluid, NE (n= 69, 129)	1	2		
Month 2: Intra-retinal fluid, No (n= 63, 129)	55	77		
Month 2: Intra-retinal fluid, Yes (n= 63, 129)	7	50		
Month 2: Intra-retinal fluid, NE (n= 63, 129)	1	2		
Month 6: Intra-retinal fluid, No (n= 60, 126)	57	85		
Month 6: Intra-retinal fluid, Yes (n= 60, 126)	1	38		
Month 6: Intra-retinal fluid, NE(n= 60, 126)	2	3		
Month 12: Intra-retinal fluid, No (n= 61, 124)	58	96		
Month 12: Intra-retinal fluid, Yes (n= 61, 124)	2	26		

Month 12: Intra-retinal fluid, NE (n= 61, 124)	1	2		

Statistical analyses

Statistical analysis title	Presence vs. absence of intra-retinal fluid
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	49.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.62
upper limit	213.5

Primary: Change in Central subfield thickness (CSFT)

End point title	Change in Central subfield thickness (CSFT)

End point description:

Central subfield thickness (CSFT) from optical coherence tomography (OCT) was assessed at screening (14 to 3 days before baseline visit), month 2, month 6 and month 12. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of change in CSFT versus previous visit. For retreated patients, the change in CSFT was considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis. *NE = Not evaluable
Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients undergoing OCT during that time point.

End point type	Primary

End point timeframe:

Screening, Month 2, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: micromilimeter(um)				
arithmetic mean (standard deviation)				
Month 2 Vs. Screening : CSFT (n= 61, 125)	-16.15 (± 86.65)	-34.28 (± 78.01)		

Month 6 Vs. Month 2: CSFT (n= 57, 121)	-11.04 (± 61.06)	-15.83 (± 70.74)		
Month 12 Vs. Month 6: CSFT (n= 57, 119)	1.29 (± 62.55)	8.64 (± 76.79)		

Statistical analyses

Statistical analysis title	Change in CST vs previous vist
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1514
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1

Primary: Change in Central subfield volume (CSV)

End point title	Change in Central subfield volume (CSV)

End point description:

Central subfield volume (CSV) from optical coherence tomography (OCT) was assessed at screening (14 to 3 days before baseline visit), month 2, month 6 and month 12. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of change in CSV versus previous visit. For retreated patients, the change in CSV was considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis. *NE = Not evaluable
Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients undergoing OCT during that time point.

End point type	Primary

End point timeframe:

Screening, Month 2, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: mm^3				
arithmetic mean (standard deviation)				
Month 2 Vs. Screening : CSV (n= 49, 96)	-0.02 (± 0.06)	-0.02 (± 0.06)		

Month 6 Vs. Month 2: CSV (n= 48, 97)	0 (± 0.04)	-0.01 (± 0.07)		
Month 12 Vs. Month 6: CSV (n= 49, 101)	0 (± 0.04)	0.01 (± 0.08)		

Statistical analyses

Statistical analysis title	Change in Central subfield volume vs previous vist
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1265
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	5.63

Primary: Number of patients treated and re-treated based on presence/absence of sub-retinal fluid

End point title	Number of patients treated and re-treated based on presence/absence of sub-retinal fluid[1]

End point description:

Presence of sub-retinal fluid from optical coherence tomography (OCT) was assessed at screening (14 to 3 days before baseline visit), month 2, month 6 and month 12. The regression model for sub-retinal fluid was not valid because “Yes” was reported in almost all subjects causing a quasi-complete separation of data points. *NE = Not Evaluable
Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients undergoing OCT during that time point.

End point type	Primary

End point timeframe:

Screening, Month 2, Month 6, Month 12

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The regression model for sub-retinal fluid was not valid hence no analysis.

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Screening: Sub-retinal fluid, No (n= 69, 129)	43	65		
Screening: Sub-retinal fluid, Yes (n= 69, 129)	25	61		

Screening: Sub-retinal fluid, NE (n= 69, 129)	1	3		
Month 2: Sub-retinal fluid, No (n= 63, 129)	58	108		
Month 2: Sub-retinal fluid, Yes (n= 63, 129)	2	17		
Month 2: Sub-retinal fluid, NE (n= 63, 129)	3	4		
Month 2: Sub-retinal fluid, Missing (n= 63, 129)	0	0		
Month 6: Sub-retinal fluid, No (n= 60, 126)	58	109		
Month 6: Sub-retinal fluid, Yes (n= 60, 126)	0	14		
Month 6: Sub-retinal fluid, NE(n= 60, 126)	2	3		
Month 12: Sub-retinal fluid, No (n= 61, 124)	60	113		
Month 12: Sub-retinal fluid, Yes (n= 61, 124)	0	8		
Month 12: Sub-retinal fluid, NE (n= 61, 124)	1	3		

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients treated and re-treated based on presence/absence of Clinically significant abnormalities

End point title	Number of patients treated and re-treated based on presence/absence of Clinically significant abnormalities

End point description:

Presence of clinically significant abnormalities was assessed at baseline, month 1, month 2, month 3, month 6 and month 12. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of presence of clinically significant abnormalities (Yes/No). For retreated patients, the presence/absence of clinically significant abnormalities was considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis. Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients undergoing ocular examination during that time point.

End point type	Primary

End point timeframe:

Baseline, Month 1, Month 2, Month 3, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Baseline: Clinically Significant Abnormal, No	61	103		

Baseline: Clinically Significant Abnormal, Yes	9	27		
Baseline: Clinically Significant Abnormal, Missing	0	0		
Month 1: Clinically Significant Abnorma, No	60	106		
Month 1: Clinically Significant Abnormal, Yes	6	24		
Month 1: Clinically Significant Abnormal, Missing	4	0		
Month 2: Clinically Significant Abnormal, No	60	103		
Month 2: Clinically Significant Abnormal, Yes	5	26		
Month 2:Clinically Significant Abnormal, Missing	5	1		
Month 3: Clinically Significant Abnormal, No	56	108		
Month 3: Clinically Significant Abnormal, Yes	7	20		
Month 3: Clinically Significant Abnormal, Missing	7	2		
Month 6: Clinically Significant Abnormal, No	59	110		
Month 6: Clinically Significant Abnormal, Yes	3	18		
Month 6: Clinically Significant Abnormal, Missing	8	2		
Month 12: Clinically Significant Abnormal, No	61	116		
Month 12: Clinically Significant Abnormal, Yes	2	12		
Month 12: Clinically Significant Abnormal, Missing	7	2		

Statistical analyses

Statistical analysis title	Clinically significant abnormalities
Statistical analysis description:	
Presence vs. absence of clinically significant abnormalities	
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0103
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.58
upper limit	30.23

Primary: Number of patients treated and re-treated based on improvement in best corrective visual acuity (BCVA) < 5 letters

End point title	Number of patients treated and re-treated based on improvement in best corrective visual acuity (BCVA) < 5 letters

End point description:

Improvement in BCVA < 5 letters (Yes/No) was assessed at month1, month 2, month 3, month 6 and month 12. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of improvement in BCVA < 5 letters (Yes/No) which was reported as Gain >= 5 letters versus Gain < 5 letters. For retreated patients, Gain >= 5 letters and Gain < 5 letters were considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis.
Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients with improvement in BCVA < 5 letters from baseline to that time point.

End point type	Primary

End point timeframe:

Baseline, Month1, Month 2, Month 3, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Month 1: Gain >= 5 letters (n= 51, 97)	37	69		
Month 1: Gain < 5 letters (n= 51, 97)	14	28		
Month 2: Gain >= 5 letters (n= 50, 95)	38	70		
Month 2: Gain < 5 letters (n= 50, 95)	12	25		
Month 3: Gain >= 5 letters (n= 52, 94)	37	74		
Month 3: Gain < 5 letters (n= 52, 94)	15	20		
Month 6: Gain >= 5 letters (n= 48, 92)	40	70		
Month 6: Gain < 5 letters (n= 48, 92)	8	22		
Month 12: Gain >= 5 letters (n= 51, 92)	43	69		
Month 12: Gain < 5 letters (n= 51, 92)	8	23		

Statistical analyses

Statistical analysis title	Gain < 5 letters vs. Gain >= 5 letters
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0854
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	5.33

Primary: Number of patients treated and re-treated based on improvement in best corrective visual acuity (BCVA) < 10 letters

End point title	Number of patients treated and re-treated based on improvement in best corrective visual acuity (BCVA) < 10 letters

End point description:

Improvement in BCVA < 10 letters (Yes/No) was assessed at month1, month 2, month 3, month 6 and month 12. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of improvement in BCVA < 10 letters (Yes/No) which was reported as Gain >= 10 letters versus Gain < 10 letters. For retreated patients, Gain >= 10 letters and Gain < 10 letters were considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value on the scheduled assessment, the value was considered as missing for this analysis. Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. 'n' represents number of patients with improvement in BCVA < 10 letters from baseline to that time point.

End point type	Primary

End point timeframe:

Baseline, Month1, Month 2, Month 3, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Month 1: Gain >= 10 letters (n= 51, 97)	13	27		
Month 1: Gain < 10 letters (n= 51, 97)	38	70		
Month 2: Gain >= 10 letters (n= 50, 95)	20	40		
Month 2: Gain < 10 letters (n= 50, 95)	30	55		
Month 3: Gain >= 10 letters (n= 52, 94)	22	41		
Month 3: Gain < 10 letters (n= 52, 94)	30	53		
Month 6: Gain >= 10 letters (n= 48, 92)	29	50		
Month 6: Gain < 10 letters (n= 48, 92)	19	42		

Month 12: Gain >= 10 letters (n= 51, 92)	28	48		
Month 12: Gain < 10 letters (n= 51, 92)	23	44		

Statistical analyses

Statistical analysis title	Gain < 10 letters vs. Gain >= 10 letters
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0114
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.23
upper limit	5.17

Primary: Number of patients in different categories of changes from baseline in BCVA

End point title	Number of patients in different categories of changes from baseline in BCVA

End point description:

Changes from baseline in BCVA are described for the ETDRS parameter considering the following categories at each assessment: “no change” if the change was equal to 0 letter, “worsening” if change < 0 letter , "improvement" if change > 0 letter. A univariate logistic regression model was applied expressing the presence/absence of the first retreatment in function of change from baseline in BCVA (improved/worsened/stable) which was reported as Improved versus no change and worsened versus no change. For retreated patients, this variable was considered at the closest time-point to the first re-treatment: the last scheduled assessment immediately before the first re-treatment was considered. For treated patients, the last scheduled assessment available was considered. In case of missing value, the value was considered as missing for this analysis. 'n' represents number of patients in FAS set with evaluable BCVA at baseline and that time point.

End point type	Primary

End point timeframe:

Baseline, Month1, Month 2, Month 3, Month 6, Month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: Patients				
Month 1: No change (n= 66, 130)	7	18		

Month 1: Worsening (n= 66, 130)	8	15		
Month 1: Improvement (n= 66, 130)	51	97		
Month 2: No change (n= 65, 129)	6	9		
Month 2: Worsening (n= 65, 129)	9	25		
Month 2: Improvement (n= 65, 129)	50	95		
Month 3: No change (n= 63, 128)	3	9		
Month 3: Worsening (n= 63, 128)	8	25		
Month 3: Improvement (n= 63, 128)	52	94		
Month 6: No change (n= 62, 128)	5	6		
Month 6: Worsening (n= 62, 128)	9	30		
Month 6: Improvement (n= 62, 128)	48	92		
Month 12: No change (n= 63, 128)	3	7		
Month 12: Worsening (n= 63, 128)	9	29		
Month 12: Improvement (n= 63, 128)	51	92		

Statistical analyses

Statistical analysis title	Change from BL in BCVA: Improved vs. No change
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0049
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.91

Statistical analysis title	Change from BL in BCVA: Worsened vs. No change
Comparison groups	Ranibizumab: Treated Once v Ranibizumab: Re-treated Once
Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0461
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	44.52

Secondary: Mean change in Best Corrected Visual Acuity (BCVA) from baseline to Month 6 and month 12 on study eye

End point title	Mean change in Best Corrected Visual Acuity (BCVA) from baseline to Month 6 and month 12 on study eye

End point description:

Change from baseline in BCVA (Best Corrected Visual Acuity) was Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score. Patients with a BCVA ETDRS letter score of 78 to 24 in the study eye were included; A higher score represents better functioning of the study eye. A positive change from baseline shows improvement. Full Analysis Set (FAS): all patients who received at least one dose of ranibizumab. The study eyes of the patients belong to FAS were analyzed.

End point type	Secondary

End point timeframe:

Baseline, month 6, month 12

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	200			
Units: letters				
arithmetic mean (standard deviation)				
Change at 6 month (n=190)	7.51 (± 11.68)			
Change at 12 month (n=191)	8.42 (± 12.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of ranibizumab injection

End point title	Mean number of ranibizumab injection

End point description:

Mean number of ranibizumab injection is reported as number of injections per patient. Full Analysis Set (FAS): all subjects who received at least one dose of ranibizumab

End point type	Secondary

End point timeframe:

baseline to month 12

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	200			
Units: number of injections				
arithmetic mean (standard deviation)	2.41 (± 1.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to re-treatment

End point title	Time to re-treatment

End point description:

Time to re-treatment, defined as time in months from the data of first dose of ranibizumab to the date of re-treatment, was evaluated. Full Analysis Set (FAS): all subjects who received at least one dose of ranibizumab

End point type	Secondary

End point timeframe:

Baseline to Month 12

End point values	Ranibizumab: Re-treated Once			
Subject group type	Subject analysis set			
Number of subjects analysed	130			
Units: Months				
arithmetic mean (standard deviation)	2.56 (± 2.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients having ocular and/or systemic adverse event (AE)

End point title	Number of patients having ocular and/or systemic adverse event (AE)

End point description:

Number of patients with any systemic AE, with serious systemic AE, with an ocular AE, with an ocular serious AE are reported. Safety Population: all subjects who received at least one dose of ranibizumab and had at least one post-baseline safety assessment

End point type	Secondary

End point timeframe:

baseline to month 12

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	200			
Units: Patients				
Any systemic Adverse Event	30			
Serious systemic Adverse Event	5			
Ocular Adverse Event	41			
Ocular serious adverse event	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in patient quality of life from baseline to month 2 and month 12

End point title	Change in patient quality of life from baseline to month 2 and month 12

End point description:

Patient quality of life was assessed by Impact of Vision Impairment (IVI) questionnaire. IVI is a 32-item instrument, either self- or interviewer-administered, developed to measure the impact of vision impairment on daily activities in five domains. The 32 items were divided into 5 domains as follows: Leisure and work (items 1 to 5), Social and consumer interaction (items 6 to 10 and items 23-24), Household and personal care (items 11 to 14 and items 20-21), Mobility (items 15 to 19 and item 22), Emotional reaction to vision loss (items 25 to 32). Responses to the IVI items were rated on a five-category Likert scale: not at all, 0; hardly at all, 1; a little, 2; a fair amount, 3; a lot, 4; and can’t do because of eyesight, 5. Total score was an arithmetic average of the items rated between 0 (the best score) and 5 (the worst score). A negative change indicates improvement. Data was computed on items with non missing response.

End point type	Secondary

End point timeframe:

Baseline, month 2, month 12

End point values	Ranibizumab: Treated Once	Ranibizumab: Re-treated Once		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	70	130		
Units: units on a scale				
arithmetic mean (standard deviation)				
Change at Month 2 (n= 60, 124)	-0.4 (± 0.68)	-0.15 (± 0.6)		
Change at month 12 (n= 59, 122)	-0.54 (± 0.91)	-0.36 (± 0.81)		

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 are reported in this record from First Patient First Treatment until Last Patient Last Visit.(up to 12 months)

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

Reporting group description:

Patients treated with a single ranibizumab 0.5 mg/0.05ml intravitreal injection. Further injections might be required when monitoring reveals disease activity.

Serious adverse events	Ranibizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 200 (3.50%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Expired product administered (Study Eye)			
subjects affected / exposed	2 / 200 (1.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Ovarian cyst			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Klebsiella sepsis			
subjects affected / exposed	1 / 200 (0.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Ranibizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 200 (13.00%)		
Eye disorders			
Choroidal neovascularisation (Non-study Eye)			
subjects affected / exposed	3 / 200 (1.50%)		
occurrences (all)	3		
Choroidal neovascularisation (Study Eye)			
subjects affected / exposed	7 / 200 (3.50%)		
occurrences (all)	9		
Conjunctival haemorrhage (Study Eye)			

subjects affected / exposed	4 / 200 (2.00%)		
occurrences (all)	4		
Conjunctival hyperaemia (Both Eyes)			
subjects affected / exposed	5 / 200 (2.50%)		
occurrences (all)	6		
Ocular hypertension (Both Eyes)			
subjects affected / exposed	4 / 200 (2.00%)		
occurrences (all)	4		
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 200 (3.50%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2014	- The amendment made some laboratory evaluations (high sensivity C-reactive protein - hsCRP, serum amyloid associated protein - SAA, C3 and C4, S100, fibrinogen) optional due to the difficulties in performing these assessments at several sites. - Minor revisions were made with regard to inclusion criteria (eligibility in bilateral mCNV patients), exclusion criteria (definition of pregnancy), concomitant medications and reference therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported