Clinical trial results:
A 12-month, prospective, multicenter, open-label, single arm, interventional study assessing the safety and tolerability of 0.5 mg ranibizumab in mono/bilateral wet AMD patients in eyes with BCVA below 2/10 and/or second affected eye

Summary

EudraCT number	2013-003333-15
Trial protocol	IT
Global end of trial date	15 June 2016

Results information

Result version number	v1 (current)
This version publication date	01 July 2017
First version publication date	01 July 2017

Trial information

Trial identification

Sponsor protocol code	CRFB002AIT02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01986907
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	Study Director, 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	11 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 June 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the annual incidence rate of both ocular and systemic drug-related adverse events (AE) following ranibizumab treatment in subjects diagnosed with wet AMD and Best Corrected Visual Acuity (BCVA) < 2/10 and/or second eye affected, regardless of BCVA.
In order to provide the most comprehensive and objective ranibizumab-related AE profile, the primary analysis was extended to include not only AEs with causal relationship established by the Investigators, but also all AEs possibly related to ranibizumab as per latest Periodic Safety Update Report (PSUR) and Risk Management Plan (RMP), AEs hereinafter referred to as Adverse Events of Special Interest (AESI).

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	04 March 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 936
Worldwide total number of subjects	936
EEA total number of subjects	936

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)	33
From 65 to 84 years	695
85 years and over	208

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 944 screened patients, nine hundred forty-one (941) subjects were enrolled in the study and 936 were treated with ranibizumab at least once. Seven hundred seventy-four (774) subjects completed the study.

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 0.5mg ranibizumab

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

Injection

Number of subjects in period 1	Ranibizumab
Started	936
Completed	769
Not completed	167
Adverse event, serious fatal	9
Consent withdrawn by subject	76
Adverse event, non-fatal	11
Did not receive study drug	5
Lost to follow-up	38
Lack of efficacy	24
Protocol deviation	4

Baseline characteristics

Reporting groups	
Reporting group title	Ranibizumab
Reporting group description: patients treated with 0.5mg ranibizumab	

Reporting group values	Ranibizumab	Total	
Number of subjects	936	936	
Age Categorical Units: Subjects			
18<65 years	33	33	
65-<85 years	695	695	
>=85 years	208	208	
Age Continuous Units: years			
arithmetic mean	78.68		
standard deviation	± 7.34	-	
Gender, Male/Female Units: Subjects			
Female	582	582	
Male	354	354	

End points

End points reporting groups

Reporting group title	Ranibizumab
Reporting group description: patients treated with 0.5mg ranibizumab	

Primary: Number of participants with systemic drug-related adverse events by SOC and PT

End point title	Number of participants with systemic drug-related adverse events by SOC and PT[1]
End point description: Monitoring and recording all adverse events, including serious adverse events.	
End point type	Primary
End point timeframe: Baseline to 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: no statistical analysis as this is a single arm study

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	936			
Units: Eyes naive to Ranibizumab				
Serious Adverse Events	3			
Non Serious Adverse Events	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of eyes with ocular drug-related adverse events

End point title	Number of eyes with ocular drug-related adverse events[2]
End point description: Monitoring and recording all adverse events, including serious adverse events.	
End point type	Primary
End point timeframe: Baseline to Month 12	

Notes:

[2] - 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: no statistical analysis as this is a single arm study.

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	936			
Units: Eyes				
Serious Adverse Events	1			
Non Serious Adverse Events	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean number of ranibizumab injections

End point title	Mean number of ranibizumab injections

End point description:

Treatment patterns for ranibizumab in the study population is described by the overall number of injections (mean, standard deviation, median, 25th and 75th percentiles, minimum and maximum), number of visits, time-interval between injections in bilateral disease, number and reasons for retreatment, number and reasons for treatment terminations.

End point type	Secondary

End point timeframe:

Baseline to month 12

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	936			
Units: injections				
arithmetic mean (standard deviation)	5.97 (± 3.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time interval between injections in bilateral disease

End point title	Time interval between injections in bilateral disease

End point description:

Mean number of days between two consecutive injections per eye (Treated eyes naïve to Ranibizumab, N=771 Eyes)

End point type	Secondary

End point timeframe:

Baseline to month 12

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	771			
Units: days				
arithmetic mean (standard deviation)	51.94 (± 26.56)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of injections

End point title	Number of injections

End point description:

Number of injections per patient. The reason for re-treatment was (accordingly with SmPC) All subjects were to be treated as per approved label: treatment was given monthly until maximum Visual Acuity (VA) was achieved (i.e. stable VA for three consecutive months). Thereafter, subjects were monitored for visual acuity and treatment was to be resumed in case of VA loss due to disease activity.

End point type	Secondary

End point timeframe:

Baseline to month 12

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	936			
Units: injections				
01	28			
02	56			
03	203			
04	103			
05	108			
06	118			
07	74			
08	50			
09	57			
10	38			
11	26			
12	21			
13	27			
14	5			
15	7			
16	1			
17	4			
18	2			
19	1			
20	1			
21	1			

22	1			
23	1			
24	1			
25	3			
26	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Ranibizumab 0.5 mg
Reporting group description:	
Ranibizumab 0.5 mg	

Serious adverse events	Ranibizumab 0.5 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	63 / 936 (6.73%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			
subjects affected / exposed	3 / 936 (0.32%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Metastases to central nervous system			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer recurrent			

subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Mastectomy			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transurethral prostatectomy			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	2 / 936 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Pneumothorax				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	2 / 936 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pulmonary oedema				
subjects affected / exposed	2 / 936 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Respiratory disorder				

subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur fracture				
subjects affected / exposed	7 / 936 (0.75%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic injury				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				

Angina pectoris				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 936 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	3 / 936 (0.32%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 2			
Myocardial infarction				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Myocardial ischaemia				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Cerebral haemorrhage				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				

subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	2 / 936 (0.21%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	3 / 936 (0.32%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 936 (0.21%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Bone marrow disorder			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Ocular hypertension				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal haemorrhage				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Faecaloma				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal haemorrhage				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	2 / 936 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar hernia				

subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal cyst			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			

subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	2 / 936 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Escherichia sepsis				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Herpes zoster				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 936 (0.53%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 936 (0.11%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sepsis				

subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Urinary tract infection			
subjects affected / exposed	1 / 936 (0.11%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 936 (0.11%)		
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 0.5 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 936 (8.12%)		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 936 (1.07%)		
occurrences (all)	10		
Eye disorders			
Cataract			
subjects affected / exposed	10 / 936 (1.07%)		
occurrences (all)	13		
Conjunctival haemorrhage			
subjects affected / exposed	13 / 936 (1.39%)		
occurrences (all)	13		
Neovascular age-related macular degeneration			
subjects affected / exposed	34 / 936 (3.63%)		
occurrences (all)	39		
Infections and infestations			
Influenza			

subjects affected / exposed occurrences (all)	15 / 936 (1.60%) 17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Single arm study does not have Statistical Analysis

Notes: