Clinical trial results:
An open-label, multi-center, expanded access program of ranibizumab in patients with visual impairment due to diabetic macular edema for whom no suitable therapeutic alternatives exist.

Summary

EudraCT number	2011-002731-26
Trial protocol	IT
Global end of trial date	08 October 2013

Results information

Result version number	v1 (current)
This version publication date	17 December 2020
First version publication date	17 December 2020

Trial information

Trial identification

Sponsor protocol code	CRFB002DIT01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 +39 02 96541,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 +39 02 96541,

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	08 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To provide early access to ranibizumab in patients with macular edema and visual impairment secondary to diabetes mellitus for whom no suitable therapeutic alternatives exist (i.e. existing therapies, e.g. laser photocoagulation, have failed or are not indicated).

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	07 November 2011
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: 617
Worldwide total number of subjects	617
EEA total number of subjects	617

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)	275
From 65 to 84 years	338

85 years and over	4

Subject disposition

Recruitment

Recruitment details:

A total of 620 subjects were screened and 617 subjects were enrolled in the study.

Pre-assignment

Screening details:

Subjects were enrolled at 33 sites in Italy. The first subject was screened on 7 November 2011. The last study visit occurred on 8 October 2013

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	Overall Study

Arm description:

Subjects received 0.5 mg ranibizumab intravitreal injection according to the approved label: the treatment was given monthly until maximum visual acuity (VA) was achieved (the subjects VA was stable for three consecutive monthly assessments).

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects received 0.5 mg ranibizumab as intravitreal injection monthly until maximum VA was achieved.

Number of subjects in period 1	Overall Study
Started	617
Completed	515
Not completed	102
Adverse event, serious fatal	3
Consent withdrawn by subject	32
Subject's condition not required program drug	4
Adverse event, non-fatal	19
Protocol violation	8
Unsatisfactory therapeutic effect	8
Lost to follow-up	27
Abnormal test procedure result(s)	1

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	617	617	
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	65.525		
standard deviation	± 9.145	-	
Gender categorical			
Please note, the data in the CSR that was provided for the gender was for the Full Analysis Set (FAS), 612. All other Baseline categories were supplied for the Enrolled patient (617). Data was provided for the actual number of subjects enrolled in the study by gender for consistency.			
Units: Subjects			
Female	228	228	
Male	389	389	

End points

End points reporting groups

Reporting group title	Overall Study

Reporting group description:

Subjects received 0.5 mg ranibizumab intravitreal injection according to the approved label: the treatment was given monthly until maximum visual acuity (VA) was achieved (the subjects VA was stable for three consecutive monthly assessments).

Primary: Percentage of Subjects Experiencing any Serious Adverse Events (SAEs)

End point title	Percentage of Subjects Experiencing any Serious Adverse Events (SAEs)[1]

End point description:

End point type	Primary

End point timeframe:

Baseline up to end of program (Up to approximately 23 months)

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 was planned or performed.

End point values	Overall Study			
Subject group type	Reporting group			
Number of subjects analysed	612[2]			
Units: Percentage of subjects				
number (not applicable)	29			

Notes:

[2] - All subjects who received at least one dose of ranibizumab and had at least one post-baseline safety

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline up to end of program (Up to approximately 23 months)	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.0
Reporting groups	
Reporting group title	Unilateral DME
Reporting group description: Unilateral DME	
Reporting group title	Bilateral DME
Reporting group description: Bilateral DME	

Serious adverse events	Unilateral DME	Bilateral DME	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 157 (4.46%)	22 / 455 (4.84%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder papilloma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal neoplasm			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			

subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial disorder			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Inflammation			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleurisy			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			

subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 157 (0.00%)	3 / 455 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Congestive cardiomyopathy			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ocular hypertension			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urethral obstruction			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Unilateral DME	Bilateral DME	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 157 (3.18%)	30 / 455 (6.59%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 157 (0.00%)	2 / 455 (0.44%)	
occurrences (all)	0	2	
Hypertensive crisis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cataract operation			
subjects affected / exposed	0 / 157 (0.00%)	2 / 455 (0.44%)	
occurrences (all)	0	2	
Cholecystectomy			

subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Toxicity to various agents			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Presyncope			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 157 (1.27%)	4 / 455 (0.88%)	
occurrences (all)	3	4	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Conjunctivitis			

subjects affected / exposed	2 / 157 (1.27%)	0 / 455 (0.00%)	
occurrences (all)	2	0	
Diabetic retinal oedema			
subjects affected / exposed	0 / 157 (0.00%)	6 / 455 (1.32%)	
occurrences (all)	0	6	
Diabetic retinopathy			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Lacrimation increased			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Macular ischaemia			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Macular oedema			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Ocular hypertension			
subjects affected / exposed	1 / 157 (0.64%)	1 / 455 (0.22%)	
occurrences (all)	1	1	
Retinal exudates			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Uveitis			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Vitreous haemorrhage			
subjects affected / exposed	1 / 157 (0.64%)	0 / 455 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Microalbuminuria			

subjects affected / exposed	0 / 157 (0.00%)	1 / 455 (0.22%)	
occurrences (all)	0	1	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 157 (0.00%)	3 / 455 (0.66%)	
occurrences (all)	0	3	
Labyrinthitis			
subjects affected / exposed	0 / 157 (0.00%)	2 / 455 (0.44%)	
occurrences (all)	0	2	

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

None reported