Clinical trial results:
24-month, multicenter, open-label, phase IIIb study to assess the efficacy and safety of Lucentis® (ranibizumab 0.5 mg) in diabetic patients presenting with reduced visual acuity due to diabetic macular edema and evaluating spacing out of follow-up after initial intensive treatment phase.

Summary

EudraCT number	2013-002850-54
Trial protocol	FR
Global end of trial date	29 April 2015

Results information

Result version number	v1 (current)
This version publication date	30 April 2016
First version publication date	30 April 2016

Trial information

Trial identification

Sponsor protocol code	CRFB002DFR11

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02032173
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,
Sponsor organisation name	Novartis Pharma AG
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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	29 April 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary study objective was to evaluate the proportion of patients presenting with stable BCVA after 24 months compared to the BCVA value observed at 6 months (difference :S 4 letters lost between the BCVA scores recorded at 6 and 24 months) when the follow-up period is spaced out after an intensive treatment phase

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	19 May 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	France: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

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)	14
From 65 to 84 years	17
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 39 patients were screened by 10 centers. 8 of the 39 screened patients were not included in the treatment phase.

Period 1

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

Arms

Arm title	Ranibizumab

Arm description:

0.5mg in 0.05ml

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

Dosage and administration details:

Ranibizumab 0.5mg

Number of subjects in period 1	Ranibizumab
Started	31
Completed	0
Not completed	31
Discontinuation due to sponsor decision	31

Baseline characteristics

Reporting groups	
Reporting group title	Ranibizumab
Reporting group description:	
0.5mg in 0.05ml	

Reporting group values	Ranibizumab	Total	
Number of subjects	31	31	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	17	17	
85 years and over	0	0	
Age Continuous | Units: Years			
arithmetic mean	64.7		
standard deviation	± 7.08	-	
Gender, Male/Female Units: Participants			
Female	10	10	
Male	21	21	

End points

End points reporting groups

Reporting group title	Ranibizumab
Reporting group description: 0.5mg in 0.05ml	

Primary: Rate of patients with a stable BCVA at 24 months compared with BCVA at 6 months

End point title	Rate of patients with a stable BCVA at 24 months compared with BCVA at 6 months[1]
End point description: Best-Corrected Visual Acuity (BCVA) is measured using an Early Treatment of Diabetic Retinopathy Study scale (ETDRS scale) at 4m. The BCVA score at 6 and 24 months visits will be used. The rate of patients with a stable BCVA (BCVA score at 6 months minus BCVA score at 24 months ≤4 letters) will be calculated as well as its confidence interval at 95%	
End point type	Primary
End point timeframe: 6 months and 24 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: Efficacy was not powered for analysis due to low enrollment. Therefore no data were analyzed for this outcome measure

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of patients with a stable BCVA at 24 months compared with BCVA at 11 months

End point title	Rate of patients with a stable BCVA at 24 months compared with BCVA at 11 months
End point description: BCVA is measured using an ETDRS scale at 4m. The BCVA score at 11 and 24 months visits will be used. The rate of patients with a stable BCVA (BCVA score at 11 months minus BCVA score at 24 months ≤4 letters) will be calculated.	
End point type	Secondary
End point timeframe: month 11 and month 24	

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of patients keeping a BCVA score gain ≥10 letters

End point title	Rate of patients keeping a BCVA score gain ≥10 letters

End point description:

The rates of patients with a BCVA score ≥10 letters for each of the following visits (months 3, 6, 8, 11, 14, 17, 20, 23 and 24) compared with baseline (day 0) will be calculated.

End point type	Secondary

End point timeframe:

baseline, months 3, 6, 8, 11, 14, 17, 20, 23 and 24

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of patients keeping a BCVA score gain ≥15 letters

End point title	Rate of patients keeping a BCVA score gain ≥15 letters

End point description:

The rates of patients with a BCVA score ≥15 letters for each of the following visits (months 3, 6, 8, 11, 14, 17, 20, 23 and 24) compared with baseline (day 0) will be calculated.

End point type	Secondary

End point timeframe:

baseline, months 3, 6, 8, 11, 14, 17, 20, 23 and 24

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: BCVA mean absolute variation from baseline to 24 months

End point title	BCVA mean absolute variation from baseline to 24 months

End point description:

BCVA scores for all visits between baseline and month 24 from both main and rescue groups are recorded. The mean absolute variations are calculated from baseline score.

End point type	Secondary

End point timeframe:

Baseline, months 1, 2, 3, 4, 5, 6, 8, 11, 14, 17, 20, 23 and 24

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: score	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Central Subfield Thickness (CST) evaluation

End point title	Central Subfield Thickness (CST) evaluation

End point description:

The absolute variations of the Central Subfield Thickness (CST) measured using a Spectral Domain-Optical Coherence Tomography (SD-OCT) at each visit is calculated from baseline score and for both main and rescue groups. Values can also be calculated as a log OCT (=log[CST/200]).

End point type	Secondary

End point timeframe:

baseline, months 1, 2, 3, 4, 5, 6, 8, 11, 14, 17, 20, 23 and 24

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	0[2]			
Units: log				
log mean (confidence interval 95%)	(to)			

Notes:

[2] - Efficacy was not powered for analysis due to low enrollment

Statistical analyses

No statistical analyses for this end point

Secondary: Effect of follow-up change on CST and BCVA in rescue group

End point title	Effect of follow-up change on CST and BCVA in rescue group

End point description:

Change of CST and BCVA score of patients from the rescue group.

End point type	Secondary

End point timeframe:

months 6, 12, 18 and 24

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: ETDRS letters				
arithmetic mean (standard deviation)	0 (± 0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of patients with a BCVA loss ≥15 letters compared with month 6

End point title	Rate of patients with a BCVA loss ≥15 letters compared with month 6

End point description:

The rate of patients with a BCVA loss ≥15 letters compared with month 6 BCVA score leading to a change of group (Rescue group) evaluated from each visit onwards stating at month 6.

End point type	Secondary

End point timeframe:

Months 6, 8, 11, 14, 17, 20, 23 and 24

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: letters	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of the spaced out follow-up on visual functions and quality of life

End point title	Evaluation of the spaced out follow-up on visual functions and quality of life

End point description:

The global score obtained on the Visual Function Questionnaire 25 (VFQ 25) will be compared from baseline to months 11 and 24 for the Main group and from baseline to months 12 and 24 for the Rescue group.

End point type	Secondary

End point timeframe:

baseline, months 11, 12 and 24

End point values	Ranibizumab			
Subject group type	Reporting group			
Number of subjects analysed	31			
Units: score	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

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	2 / 31 (6.45%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Musculoskeletal and connective tissue disorders			
Osteonecrosis			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 31 (3.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Ranibizumab 0.5 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 31 (9.68%)		

Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	 3 / 31 (9.68%) 3		

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