Clinical trial results:
Prospective, randomized, multicenter, open label phase II study to access efficacy and safety of Lucentis monotherapy (ranibizumab 0.5 mg intravitreal injections) compared with Lucentis plus panretinal photocoagulation (PRP) and PRP (monotherapy) in the treatment of patients with high risk proliferative diabetic retinopathy.

Summary

EudraCT number	2009-014409-15
Trial protocol	PT
Global end of trial date	02 December 2013

Results information

Result version number	v1 (current)
This version publication date	14 November 2020
First version publication date	14 November 2020
Summary attachment (see zip file)	Final study Report (EudraCT_2009-014409-15_Study_Report_Final_V3_20151030.pdf)

Trial information

Trial identification

Sponsor protocol code	CRFB002DPT04T

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01280929
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIBILI
Sponsor organisation address	Azinhaga de Santa Comba, Celas , Coimbra, Portugal, 3000-548
Public contact	President of Board of AIBILI and Coordinating Investigator, Prof. José Cunha Vaz, 351 239480131, lcarvalho@aibili.pt
Scientific contact	President of Board of AIBILI and Coordinating Investigator, Prof. José Cunha Vaz, 351 239480131, lcarvalho@aibili.pt

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	30 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this trial is to evaluate safety and to compare the efficacy of intravitreous injection of ranibizumab alone (0.5 mg), versus combination of intravitreous injection of ranibizumab (0.5 mg) plus PRP, versus PRP alone in the regression of retinal neovascularization in eyes with high-risk PDR.

Protection of trial subjects:

Informed consent was obtained from each subject in writing before any study procedures. The study was described by a study coordinator and/or investigator, who answered any questions, and written information was also provided. Samples of the written information were given to each subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 November 2010
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	Portugal: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	35
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period was extended from November 2010 to November 2012 (2 years). Even though, only 35 patients were recruited from the 54 initially planned.

Pre-assignment

Screening details:

Type I, or Type II diabetic subjects as defined by the WHO criteria of either, and aged ≥ 18 years.
HR-PDR eyes.
Best corrected Visual Acuity (BCVA) at screening > 20/320 (25 letters in the ETDRS Chart) in the study eye.
Clear ocular media and adequate pupillary dilatation to permit good quality fundus photography.
Intraocular pressure < 21 mmH

Pre-assignment period milestones

Number of subjects started	35
Number of subjects completed	35

Period 1

Period 1 title	baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Active Comparator: Panretinal Photocoagulation (PRP)

Arm description:

Group 1: Panretinal photocoagulation treatment (PRP) at month-0 that can be repeated after month-3.

Arm type	Comparator - Surgical Procedure

No investigational medicinal product assigned in this arm

Arm title	Experimental: Ranibizumab

Arm description:

Group 2: Intravitreous injections of ranibizumab every 4 weeks at month-0, month-1 and month-2 that can be repeated after month-3.

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

Dosage and administration details:

Intravitreous injections of ranibizumab every 4 weeks at month-0, month-1 and month-2 that can be repeated after month-3.

Arm title	Experimental: Ranibizumab + Panretinal Photocoagulation (PRP)

Arm description:

Group 3: Combination treatment of ranibizumab intravitreous injections plus PRP (2 weeks +/- 1 week after injection), at month-0, month-1 and month-2 that can be repeated after month-3.

Arm type	Combination

Investigational medicinal product name	Panretinal Photocoagulation (PRP) Drug: Intravitreous injection of ranibizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use, Ocular use

Dosage and administration details:

Combination treatment of ranibizumab intravitreous injections plus PRP (2 weeks +/- 1 week after injection), at month-0, month-1 and month-2 that can be repeated after month-3.

Number of subjects in period 1	Active Comparator: Panretinal Photocoagulation (PRP)	Experimental: Ranibizumab	Experimental: Ranibizumab + Panretinal Photocoagulation (PRP)
Started	13	10	12
Completed	11	9	10
Not completed	2	1	2
Adverse event, non-fatal	2	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Active Comparator: Panretinal Photocoagulation (PRP)
Reporting group description:	
Group 1: Panretinal photocoagulation treatment (PRP) at month-0 that can be repeated after month-3.	
Reporting group title	Experimental: Ranibizumab
Reporting group description:	
Group 2: Intravitreous injections of ranibizumab every 4 weeks at month-0, month-1 and month-2 that can be repeated after month-3.	
Reporting group title	Experimental: Ranibizumab + Panretinal Photocoagulation (PRP)
Reporting group description:	
Group 3: Combination treatment of ranibizumab intravitreous injections plus PRP (2 weeks +/- 1 week after injection), at month-0, month-1 and month-2 that can be repeated after month-3.	

Reporting group values	Active Comparator: Panretinal Photocoagulation (PRP)	Experimental: Ranibizumab	Experimental: Ranibizumab + Panretinal Photocoagulation (PRP)
Number of subjects	13	10	12
Age categorical			
Age over 18			
Units: Subjects			
Adults age over 18	13	10	12
Age continuous			
Age at screening			
Units: years			
arithmetic mean	52.7	59.9	55.1
standard deviation	± 13.6	± 6.2	± 10.6
Gender categorical			
Units: Subjects			
Female	3	4	2
Male	10	6	10

Reporting group values	Total		
Number of subjects	35		
Age categorical			
Age over 18			
Units: Subjects			
Adults age over 18	35		
Age continuous			
Age at screening			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	9		
Male	26		

Subject analysis sets	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients included in the study were used for the Intent to Treat (ITT) population analysis.	
Subject analysis set title	PP population
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients which concluded the study were used for Per Protocol (PP) population analysis.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients with at least 1 evaluation.	

Reporting group values	ITT population	PP population	Safety Population
Number of subjects	35	30	35
Age categorical			
Age over 18			
Units: Subjects			
Adults age over 18	35	30	35
Age continuous			
Age at screening			
Units: years			
arithmetic mean	55.6	54.8	55.6
standard deviation	± 11.3	± 11.7	± 11.3
Gender categorical			
Units: Subjects			
Female	9	9	9
Male	26	21	26

End points

End points reporting groups

Reporting group title	Active Comparator: Panretinal Photocoagulation (PRP)
Reporting group description:	
Group 1: Panretinal photocoagulation treatment (PRP) at month-0 that can be repeated after month-3.	
Reporting group title	Experimental: Ranibizumab
Reporting group description:	
Group 2: Intravitreous injections of ranibizumab every 4 weeks at month-0, month-1 and month-2 that can be repeated after month-3.	
Reporting group title	Experimental: Ranibizumab + Panretinal Photocoagulation (PRP)
Reporting group description:	
Group 3: Combination treatment of ranibizumab intravitreous injections plus PRP (2 weeks +/- 1 week after injection), at month-0, month-1 and month-2 that can be repeated after month-3.	
Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients included in the study were used for the Intent to Treat (ITT) population analysis.	
Subject analysis set title	PP population
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients which concluded the study were used for Per Protocol (PP) population analysis.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients with at least 1 evaluation.	

Primary: Regression of NV

End point title	Regression of NV
End point description:	
Regression of NV from screening to the 12 months visit (primary endpoint), was measured by an independent reading center in disc area (DA) units (decimal DA units), based on CFP (retinography) and FA. Regression of NV was defined as any decrease in the area of NV.	
End point type	Primary
End point timeframe:	
From screening to 12-months visit	

End point values	Active Comparator: Panretinal Photocoagulation (PRP)	Experimental: Ranibizumab	Experimental: Ranibizumab + Panretinal Photocoagulation (PRP)	ITT population
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	13	9	10	35
Units: number				
Without Regression	5	3	0	8
With Regression	8	6	10	24

End point values	PP population			
Subject group type	Subject analysis set			
Number of subjects analysed	30			
Units: number				
Without Regression	6			
With Regression	24			

Statistical analyses

Statistical analysis title	Primary Objective

Statistical analysis description:

The hypothesis was tested using the Exact Fisher test with a statistical adjustment for multiple between-treatment comparisons (i.e., PRP vs. Ranibizumab and Ranibizumab+PRP). An alpha level of 0.05 was considered (corrected to 0.016 for the 3 groups under analysis).

Comparison groups	Active Comparator: Panretinal Photocoagulation (PRP) v Experimental: Ranibizumab v Experimental: Ranibizumab + Panretinal Photocoagulation (PRP)
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.075
Method	Fisher exact
Parameter estimate	proportion
Point estimate	0.6
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.5
upper limit	0.7

Notes:

[1] - The primary objective of this study was to demonstrate superiority of one of the treatment groups: ranibizumab 0.5 mg monotherapy, PRP monotherapy or combination therapy (ranibizumab 0.5 mg plus PRP) over a 12-month treatment period in the following:
1. Regression of NV.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Screening up to 24-months (12-months of study follow-up plus 12-months post-study).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Safety Population
Reporting group description: Safety population safety reporting	
Reporting group title	Group 1
Reporting group description: Safety reporting for Group 1	
Reporting group title	Group 2
Reporting group description: Safety reporting for Group 2	
Reporting group title	Group 3
Reporting group description: Safety reporting for Group 3	

Serious adverse events	Safety Population	Group 1	Group 2
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 35 (11.43%)	0 / 13 (0.00%)	2 / 10 (20.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of adrenal gland			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Benign prostatic hyperplasia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erysipelas			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 3		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of adrenal gland			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erysipelas			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Safety Population	Group 1	Group 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 35 (57.14%)	8 / 13 (61.54%)	3 / 10 (30.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Cardiac valve disease			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Surgical and medical procedures			
Vitrectomy			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Ear and labyrinth disorders			
Preauricular cyst			
subjects affected / exposed	1 / 35 (2.86%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Diabetic retinopathy			
subjects affected / exposed	1 / 35 (2.86%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Eye pain			

subjects affected / exposed	1 / 35 (2.86%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Ocular hypertension			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Retinal detachment			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Retinal neovascularisation			
subjects affected / exposed	1 / 35 (2.86%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Ulcerative keratitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Vitreous haemorrhage			
subjects affected / exposed	10 / 35 (28.57%)	7 / 13 (53.85%)	2 / 10 (20.00%)
occurrences (all)	10	7	2
Gastrointestinal disorders			
Oral mucosal blistering			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Depression			
subjects affected / exposed	1 / 35 (2.86%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 35 (2.86%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0

Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Rhinitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Hyperuricaemia			
subjects affected / exposed	1 / 35 (2.86%)	1 / 13 (7.69%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Hypoglycaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 13 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Group 3		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cardiac disorders			
Cardiac valve disease			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Surgical and medical procedures			
Vitrectomy			
subjects affected / exposed	0 / 12 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			

Preauricular cyst subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Diabetic retinopathy subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Eye pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Ocular hypertension subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Retinal detachment subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Retinal neovascularisation subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
Ulcerative keratitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Vitreous haemorrhage subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Gastrointestinal disorders Oral mucosal blistering subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		

Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 0 / 12 (0.00%) 0		
Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0		
Infections and infestations Cystitis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Hyperuricaemia subjects affected / exposed occurrences (all) Hypoglycaemia subjects affected / exposed occurrences (all)	 0 / 12 (0.00%) 0 1 / 12 (8.33%) 1		

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.

The main limitations of this trial are the follow-up period and the reduced number of patients included in the study.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26630400