Clinical trial results:
Prospective, randomized, multicentre, open label, phase II / III study to assess efficacy and safety of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation (PRP) versus PRP in monotherapy in the treatment of subjects with high risk proliferative diabetic retinopathy. (PROTEUS)

Summary

EudraCT number	2013-003640-23
Trial protocol	GB PT
Global end of trial date	27 May 2016

Results information

Result version number	v1 (current)
This version publication date	05 July 2018
First version publication date	05 July 2018
Summary attachment (see zip file)	Study Report Synopsis (Imp16-7_3_00_Study_Report_SYNOPSIS_20161128.pdf)

Trial information

Trial identification

Sponsor protocol code	ECR-RET-2013-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01941329
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIBILI
Sponsor organisation address	Azinhaga de Santa Comba, Celas, 3000-548 Coimbra – Portugal , Coimbra, Portugal, 3000-548
Public contact	4C- Coimbra Coordinating Centre for Clinical Research , AIBILI - Association for Innovation and Biomedical Research on Light and Image, +351 2394801131, 4c@aibili.pt
Scientific contact	4C- Coimbra Coordinating Centre for Clinical Research , AIBILI - Association for Innovation and Biomedical Research on Light and Image, +351 2394801131, 4c@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	21 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2016
Global end of trial reached?	Yes
Global end of trial date	27 May 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of ranibizumab 0.5 mg intravitreal injections plus panretinal photocoagulation versus panretinal photocoagulation alone on the regression of the neovascularization area in patients with high-risk proliferative diabetic retinopathy over a 12-month treatment period.

Protection of trial subjects:

All the measures were taken to ensure subject safety. Study medication was dispensed to the subjects of the Study Group according to the study protocol. The Principal Investigator and all clinical study staff conducted the clinical study in compliance with the protocol. The Principal Investigator ensured that all personnel involved in the conduct of the study were qualified to perform their assigned responsibilities through relevant education, training and experience.
To ensure data confidentiality each subject was uniquely identified by a subject identification code. Only the Investigator was able to identify the subject based on the subject identification code.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 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	Portugal: 33
Country: Number of subjects enrolled	United Kingdom: 19
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Italy: 21
Worldwide total number of subjects	87
EEA total number of subjects	87

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)	68
From 65 to 84 years	18
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study population was recruited by each Investigator from his/her clinical practice and the planned study population was 94 patients.
The recruitment started on 28/03/2014, the FPFV was on 04/04/2014 and the LPLV was on 31/03/2015 (1 year of recruitment period).

Pre-assignment

Screening details:

Subjects who signed the informed consent form participated in a screening period, lasting 1 to 30 days, to evaluate eligibility (inclusion and exclusion criteria).
122 patients were screened (87 enrolled and 35 screening failures).

Period 1

Period 1 title	Loading Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This is an open-label study. Blinding/unblinding procedures are not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Study Group

Arm description:

The study subjects received between Month-0 and Month-2 (3-months Loading Phase) 3 ranibizumab ITV injections in Month-0, Month-1 and Month-2 combined with the standard Panretinal Photocoagulation (PRP) treatment, i.e., with 1 mandatory laser session 2 ± 1 weeks after the 1st ITV injection (Month-0) and a maximum of 2 laser sessions, one 2 ± 1 weeks after the 2nd ITV injection (Month-1) and another 2 ± 1 weeks after the 3rd ITV injection (Month-2) to complete the PRP treatment.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	S01LA04
Other name	Lucentis
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal injection of ranibizumab (0.5mg)

Arm title	Control Group

Arm description:

The control subjects received between Month-0 and Month-2 (3-months Loading Phase) the standard Panretinal Photocoagulation (PRP) treatment, with 1 mandatory laser session in Month-0 and more laser sessions as needed until Month-2 to complete the PRP treatment.

Arm type	Active comparator (surgical procedure)

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Study Group	Control Group
Started	41	46
Completed	41	45
Not completed	0	1
Lost to follow-up	-	1

Period 2

Period 2 title	Treatment Phase/Follow-up Visits
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is an open-label study. Blinding/unblinding procedures are not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Study Group

Arm description:

From Month-3 to Month-11 (9-months Follow-Up/ Treatment Phase), combination treatment composed of 1 ranibizumab ITV injection plus 1 Panretinal Photocoagulation (PRP) session (2 ± 1 weeks after the injection) could be performed respecting always at least 1 month of interval between ITV injections. In every visit, the Investigator evaluated whether treatment should be repeated. Treatment was repeated if NV was still present (due to lack of regression or due to recurrence) and if the Investigator considered that a new treatment may bring benefit to the subject and reduce the NV area. In the Follow-up PRP treatments were performed using fill-in techniques.

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	S01LA04
Other name	Lucentis
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal injection of ranibizumab (0.5mg)

Arm title	Control Group

Arm description:

From Month-3 to Month-11 (9-months Follow-Up/ Treatment Phase) patients received Panretinal Photocoagulation (PRP) as needed.

Arm type	Active comparator (surgical procedure)

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Study Group	Control Group
Started	41	45
Completed	39	38
Not completed	2	7
Adverse event, non-fatal	1	6
Lost to follow-up	-	1
Lack of efficacy	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Study Group
Reporting group description:	
The study subjects received between Month-0 and Month-2 (3-months Loading Phase) 3 ranibizumab ITV injections in Month-0, Month-1 and Month-2 combined with the standard Panretinal Photocoagulation (PRP) treatment, i.e., with 1 mandatory laser session 2 ± 1 weeks after the 1st ITV injection (Month-0) and a maximum of 2 laser sessions, one 2 ± 1 weeks after the 2nd ITV injection (Month-1) and another 2 ± 1 weeks after the 3rd ITV injection (Month-2) to complete the PRP treatment.	
Reporting group title	Control Group
Reporting group description:	
The control subjects received between Month-0 and Month-2 (3-months Loading Phase) the standard Panretinal Photocoagulation (PRP) treatment, with 1 mandatory laser session in Month-0 and more laser sessions as needed until Month-2 to complete the PRP treatment.	

Reporting group values	Study Group	Control Group	Total
Number of subjects	41	46	87
Age categorical Units: Subjects			
Adults (18-64 years)	29	39	68
From 65-84 years	11	7	18
85 years and over	1	0	1
Age continuous Units: years			
arithmetic mean	58.83	52.02	
standard deviation	± 13.32	± 11.86	-
Gender categorical Units: Subjects			
Female	13	19	32
Male	28	27	55
Neovascularization Total area Units: Disc area			
arithmetic mean	1.93	3.07	
standard deviation	± 2.21	± 5.66	-
Neovascularization in the Disc area Units: Disc area			
arithmetic mean	0.41	0.58	
standard deviation	± 1.13	± 2.00	-
Neovascularization Elsewhere area Units: Disc area			
arithmetic mean	1.51	2.49	
standard deviation	± 1.96	± 4.63	-
Best-Corrected Visual Acuity Units: Letters			
arithmetic mean	76.12	75.13	
standard deviation	± 10.39	± 10.67	-
Retinal Thickness in the Central Subfield Units: Micrometer			
arithmetic mean	292.59	300.41	

standard deviation	± 37.52	± 38.12	-
Retinal Thickness in the Inner Ring Inferior			
Units: Micrometer			
arithmetic mean	341.80	354.24	
standard deviation	± 37.20	± 37.87	-
Retinal Thickness in the Inner Ring Nasal			
Units: Micrometer			
arithmetic mean	354.88	361.83	
standard deviation	± 34.99	± 30.77	-
Retinal Thickness in the Inner Ring Superior			
Units: Micrometer			
arithmetic mean	350.37	362.58	
standard deviation	± 35.00	± 47.57	-
Retinal Thickness in the Inner Ring Temporal			
Units: Micrometer			
arithmetic mean	342.44	358.17	
standard deviation	± 40.08	± 44.43	-
Retinal Thickness in the Outer Ring Inferior			
Units: Micrometer			
arithmetic mean	303.63	311.80	
standard deviation	± 30.23	± 31.79	-
Retinal Thickness in the Outer Ring Nasal			
Units: Micrometer			
arithmetic mean	329.00	338.40	
standard deviation	± 27.05	± 33.80	-
Retinal Thickness in the Outer Ring Superior			
Units: Micrometer			
arithmetic mean	320.00	331.29	
standard deviation	± 42.07	± 49.08	-
Retinal Thickness in the Outer Ring Temporal			
Units: Micrometer			
arithmetic mean	312.68	328.67	
standard deviation	± 50.39	± 51.00	-

Subject analysis sets

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS), consistently with ICH Guideline E9, Statistical Principles for Clinical Trials, include all randomized subjects receiving at least one study treatment and having a baseline and at least one post-baseline measurements on the primary outcome (85 patients). Subjects with major entry violations likely to affect outcome were excluded by blind review. The carrying forward of the last observation, an imputation technique, was used to compensate for missing data on the primary outcome.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population defines a subset of the subjects in the FAS who are more compliant with the protocol and is characterised by the availability of measurements of the primary variable and the absence of any major protocol violations (57 patients). Only observed data was used in the PP population; i.e. missing data was not imputed.

Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis population consists of subjects who received at least one treatment (ITV injections plus PRP or PRP alone).

Reporting group values	Full Analysis Set (FAS)	Per Protocol (PP)	Safety Analysis
Number of subjects	85	57	87
Age categorical Units: Subjects			
Adults (18-64 years)	66	43	68
From 65-84 years	18	13	18
85 years and over	1	1	1
Age continuous Units: years			
arithmetic mean	55.54	56.7	55.23
standard deviation	± 12.83	± 12.32	± 12.95
Gender categorical Units: Subjects			
Female	32	19	32
Male	53	38	55
Neovascularization Total area Units: Disc area			
arithmetic mean	2.55	2.32	2.53
standard deviation	± 4.45	± 4.71	± 4.4
Neovascularization in the Disc area Units: Disc area			
arithmetic mean	0.51	0.43	0.50
standard deviation	± 1.66	± 1.13	± 1.64
Neovascularization Elsewhere area Units: Disc area			
arithmetic mean	2.04	1.89	2.03
standard deviation	± 3.68	± 4.17	± 3.64
Best-Corrected Visual Acuity Units: Letters			
arithmetic mean	75.69	76.14	75.60
standard deviation	± 10.43	± 10.20	± 10.49
Retinal Thickness in the Central Subfield Units: Micrometer			
arithmetic mean	297.54	299.02	296.72
standard deviation	± 37.88	± 37.81	± 37.83
Retinal Thickness in the Inner Ring Inferior Units: Micrometer			
arithmetic mean	348.82	346.47	348.31
standard deviation	± 38.15	± 39.38	± 37.85
Retinal Thickness in the Inner Ring Nasal			

Units: Micrometer			
arithmetic mean	358.89	357.16	358.55
standard deviation	± 33.10	± 33.80	± 32.82
Retinal Thickness in the Inner Ring Superior			
Units: Micrometer			
arithmetic mean	357.48	353.72	356.76
standard deviation	± 42.16	± 41.84	± 42.26
Retinal Thickness in the Inner Ring Temporal			
Units: Micrometer			
arithmetic mean	351.75	349.12	350.76
standard deviation	± 42.60	± 44.27	± 42.93
Retinal Thickness in the Outer Ring Inferior			
Units: Micrometer			
arithmetic mean	308.61	307.47	307.91
standard deviation	± 31.10	± 31.57	± 31.15
Retinal Thickness in the Outer Ring Nasal			
Units: Micrometer			
arithmetic mean	334.55	334.74	333.92
standard deviation	± 31.03	± 32.62	± 30.95
Retinal Thickness in the Outer Ring Superior			
Units: Micrometer			
arithmetic mean	326.70	327.47	325.91
standard deviation	± 46.19	± 51.05	± 45.96
Retinal Thickness in the Outer Ring Temporal			
Units: Micrometer			
arithmetic mean	322.27	318.21	321.05
standard deviation	± 50.92	± 50.53	± 51.05

End points

End points reporting groups

Reporting group title	Study Group

Reporting group description:

The study subjects received between Month-0 and Month-2 (3-months Loading Phase) 3 ranibizumab ITV injections in Month-0, Month-1 and Month-2 combined with the standard Panretinal Photocoagulation (PRP) treatment, i.e., with 1 mandatory laser session 2 ± 1 weeks after the 1st ITV injection (Month-0) and a maximum of 2 laser sessions, one 2 ± 1 weeks after the 2nd ITV injection (Month-1) and another 2 ± 1 weeks after the 3rd ITV injection (Month-2) to complete the PRP treatment.

Reporting group title	Control Group

Reporting group description:

The control subjects received between Month-0 and Month-2 (3-months Loading Phase) the standard Panretinal Photocoagulation (PRP) treatment, with 1 mandatory laser session in Month-0 and more laser sessions as needed until Month-2 to complete the PRP treatment.

Reporting group title	Study Group

Reporting group description:

From Month-3 to Month-11 (9-months Follow-Up/ Treatment Phase), combination treatment composed of 1 ranibizumab ITV injection plus 1 Panretinal Photocoagulation (PRP) session (2 ± 1 weeks after the injection) could be performed respecting always at least 1 month of interval between ITV injections. In every visit, the Investigator evaluated whether treatment should be repeated. Treatment was repeated if NV was still present (due to lack of regression or due to recurrence) and if the Investigator considered that a new treatment may bring benefit to the subject and reduce the NV area. In the Follow-up PRP treatments were performed using fill-in techniques.

Reporting group title	Control Group

Reporting group description:

From Month-3 to Month-11 (9-months Follow-Up/ Treatment Phase) patients received Panretinal Photocoagulation (PRP) as needed.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set (FAS), consistently with ICH Guideline E9, Statistical Principles for Clinical Trials, include all randomized subjects receiving at least one study treatment and having a baseline and at least one post-baseline measurements on the primary outcome (85 patients). Subjects with major entry violations likely to affect outcome were excluded by blind review. The carrying forward of the last observation, an imputation technique, was used to compensate for missing data on the primary outcome.

Subject analysis set title	Per Protocol (PP)
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol (PP) population defines a subset of the subjects in the FAS who are more compliant with the protocol and is characterised by the availability of measurements of the primary variable and the absence of any major protocol violations (57 patients). Only observed data was used in the PP population; i.e. missing data was not imputed.

Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis population consists of subjects who received at least one treatment (ITV injections plus PRP or PRP alone).

Primary: Neovascularization area reduction

End point title	Neovascularization area reduction

End point description:

The primary endpoint was defined as the regression of neovascularization (NV) from baseline to the 12-month visit, measured in disc area units based on Color Fundus Photography and Fluorescein Angiography. Regression of NV was defined as any decrease of the area of neovascularization.

End point type	Primary

End point timeframe:

From Baseline to the 12-month visit

End point values	Study Group	Control Group	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	44	85	
Units: 85				
Yes	38	31	69	
No	3	13	16	

Statistical analyses

Statistical analysis title	Primary efficacy analysis with ITT population

Statistical analysis description:

The null (H0) and alternative (H1) hypotheses to be tested in the primary efficacy analysis are:
H0: there is no difference between groups for the number of subjects with neovascularization reduction (at Month-12).
H1: there is a difference between groups for the number of subjects with neovascularization reduction (at Month-12).
This hypothesis will be tested using Chi-square test with two-sided Alpha = 0.05.

Comparison groups	Control Group v Study Group
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared

Primary: Neovascularization area reduction

End point title	Neovascularization area reduction

End point description:

The primary endpoint was defined as the regression of neovascularization (NV) from baseline to the 12-month visit, measured in disc area units based on Color Fundus Photography and Fluorescein Angiography. Regression of NV was defined as any decrease of the area of neovascularization.

End point type	Primary

End point timeframe:

From baseline to Month-12

End point values	Study Group	Control Group	Per Protocol (PP)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	29	28	57	
Units: 57				
Yes	27	18	45	
No	2	10	12	

Statistical analyses

Statistical analysis title	Primary efficacy analysis with PP population

Statistical analysis description:

The null (H0) and alternative (H1) hypotheses to be tested in the primary efficacy analysis are:
H0: there is no difference between groups for the number of subjects with neovascularization reduction (at Month-12).
H1: there is a difference between groups for the number of subjects with neovascularization reduction (at Month-12).
This hypothesis will be tested using Chi-square test with two-sided Alpha = 0.05.

Comparison groups	Study Group v Control Group
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Chi-squared

Secondary: Best-Corrected Visual Acuity difference

End point title	Best-Corrected Visual Acuity difference

End point description:

Best-Corrected Visual Acuity changes from baseline to Month-12.

End point type	Secondary

End point timeframe:

From baseline to Month-12

End point values	Study Group	Control Group	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	44	85	
Units: Letters				
arithmetic mean (standard deviation)	-0.90 (± 12.08)	-5.81 (± 15.08)	-3.42 (± 13.84)	

Statistical analyses

Statistical analysis title	BCVA changes
Statistical analysis description:	
Best-Corrected Visual Acuity changes from baseline to Month-12 were tested using Student’s T test	
Comparison groups	Control Group v Study Group
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided

Secondary: Time to complete neovascularization regression

End point title	Time to complete neovascularization regression
End point description:	
Survival analysis was carried out to compare time to complete neovascularization regression between groups.	
End point type	Secondary
End point timeframe:	
One year	

End point values	Study Group	Control Group	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	44	85	
Units: 85				
At month 3	29	5	34	
At month 7	3	2	5	
At month 12	1	4	5	

Statistical analyses

Statistical analysis title	Time to complete neovascularization regression
Statistical analysis description:	
Survival analysis (log-rank test) was carried out to compare Time to complete NV regression between groups.	
Comparison groups	Study Group v Control Group
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Logrank

Secondary: Recurrence of neovascularization

End point title	Recurrence of neovascularization

End point description:

Recurrence of neovascularization during the follow-up period.

End point type	Secondary

End point timeframe:

One year

End point values	Study Group	Control Group	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	44	85	
Units: 85				
Yes	27	20	47	
No	13	15	28	

Statistical analyses

Statistical analysis title	Recurrence of neovascularization

Statistical analysis description:

Recurrence of neovascularization was tested using Fisher's exact test.

Comparison groups	Study Group v Control Group
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Fisher exact

Secondary: Macular retinal thickness, assessed by OCT, difference

End point title	Macular retinal thickness, assessed by OCT, difference

End point description:

Macular retinal thickness changes from baseline to Month-12, in the central subfield, in the inner ring inferior, nasal superior and temporal, and in the outer ring inferior, nasal superior and temporal.

End point type	Secondary

End point timeframe:

From baseline to Month-12

End point values	Study Group	Control Group	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	44	85	
Units: µm				
arithmetic mean (standard deviation)				
In the Central Subfield	7 (± 33.49)	21.68 (± 75.26)	14.6 (± 59.06)	
In the Inner Ring Inferior	4.07 (± 61.55)	18.6 (± 57.35)	11.51 (± 59.53)	
In the Inner Ring Nasal	7.93 (± 65.12)	21.32 (± 56.32)	14.86 (± 60.73)	
In the Inner Ring Superior	0.66 (± 19.94)	11.51 (± 45.24)	6.21 (± 35.46)	
In the Inner Ring Temporal	0.73 (± 32.08)	8.23 (± 52.1)	4.61 (± 43.52)	
In the outer ring inferior	-1.32 (± 18.98)	13.6 (± 41.92)	6.32 (± 33.45)	
in the outer ring nasal	4.15 (± 27.11)	14.4 (± 52.46)	9.39 (± 42.11)	
in the outer ring superior	4.93 (± 45.23)	5.72 (± 38.12)	5.33 (± 41.49)	
in the outer ring temporal	-0.73 (± 35.63)	6.88 (± 37.96)	3.17 (± 36.82)	

Statistical analyses

Statistical analysis title	Macular retinal thickness changes

Statistical analysis description:

Macular retinal thickness changes from baseline to Month-12 for the study and control groups were tested using Student's T test.

Comparison groups	Study Group v Control Group
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided

Secondary: Need of treatment for Diabetic Macular Edema

End point title	Need of treatment for Diabetic Macular Edema

End point description:

Subjects that needed treatment for DME in the control group and in the study group.

End point type	Secondary

End point timeframe:

One year.

End point values	Study Group	Control Group	Safety Analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	44	87	
Units: 85				
Yes	0	2	2	
No	41	42	85	

Statistical analyses

Statistical analysis title	Need of treatment for DME

Statistical analysis description:

Need of treatment for DME was tested using Fisher's exact test.

Comparison groups	Study Group v Control Group
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Fisher exact

Secondary: Need of vitrectomy

End point title	Need of vitrectomy

End point description:

Need of vitrectomy due to the occurrence of vitreous hemorrhage, tractional retinal detachment or other complications of Diabetic Retinopathy.

End point type	Secondary

End point timeframe:

One year.

End point values	Study Group	Control Group	Safety Analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	41	44	87	
Units: 85				
Yes	1	5	6	
No	40	39	81	

Statistical analyses

Statistical analysis title	Need of vitrectomy

Statistical analysis description:

Need of vitrectomy due to the occurrence of vitreous haemorrhage, tractional retinal detachment or other complications of Diabetic Retinopathy was tested using Fisher's exact test.

Comparison groups	Control Group v Study Group
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events reported by the subject (spontaneously or via study interview) were collected from the first day until 30 days after discontinuation/completion of study participation even if the event was not considered to be related to study drug.

Adverse event reporting additional description:

In case of Serious Adverse Events (SAEs), the Investigator immediately reported to the Sponsor all SAEs with the exception of those that were identified as not requiring immediate reporting in protocol. The Investigator filled in a SAE Form within 24 hours of learning of its occurrence.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Study Group

Reporting group description:

Patients received Ranibizumab and Standard PRP (Panretinal Photocoagulation) (2±1 weeks after ITV).

Reporting group title	Control Group

Reporting group description:

Patients received Standard PRP (panretinal photocoagulation)

Serious adverse events	Study Group	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 41 (12.20%)	7 / 46 (15.22%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Surgical and medical procedures			
Back surgery			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Below knee amputation			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stem cell transplant			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 41 (0.00%)	2 / 46 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypoglycaemic coma			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (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	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Subretinal haemorrhage			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
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	1 / 41 (2.44%)	3 / 46 (6.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			

subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot ulcer			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
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			
Slipped disc			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Epididymitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Food intolerance			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Study Group	Control Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 41 (51.22%)	21 / 46 (45.65%)	
Vascular disorders			
Hypertension arterial			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Peripheral vascular disease			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Coronary stent placement			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Eye operation NOS			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Intraocular lens implant			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Phacoemulsification			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Vitrectomy			
subjects affected / exposed	2 / 41 (4.88%)	1 / 46 (2.17%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 41 (2.44%)	1 / 46 (2.17%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			

Benign prostatic hypertrophy			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Investigations			
Blood urea nitrogen abnormal			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Gamma GT raised			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Intraocular pressure high			
subjects affected / exposed	2 / 41 (4.88%)	4 / 46 (8.70%)	
occurrences (all)	3	4	
Serum creatinine increased			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Corneal abrasion			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Wound dehiscence			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Phantom limb pain			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Tingling feet/hands			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Leukocytosis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Pancytopenia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear ache			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Allergic conjunctivitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Anterior uveitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Cataract			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Cataract cortical			
subjects affected / exposed	0 / 41 (0.00%)	2 / 46 (4.35%)	
occurrences (all)	0	3	
Cataract nuclear			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Diabetic macular edema			
subjects affected / exposed	1 / 41 (2.44%)	2 / 46 (4.35%)	
occurrences (all)	1	2	
Dry Eyes			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Hypertension ocular			

subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Macular fibrosis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Panuveitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Proliferative diabetic retinopathy			
subjects affected / exposed	2 / 41 (4.88%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Retinal detachment			
subjects affected / exposed	0 / 41 (0.00%)	2 / 46 (4.35%)	
occurrences (all)	0	2	
Rubeosis iridis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Subretinal haemorrhage			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Uveitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Visual acuity decreased			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Vitreous floater			
subjects affected / exposed	0 / 41 (0.00%)	2 / 46 (4.35%)	
occurrences (all)	0	2	
Vitreous haemorrhage			
subjects affected / exposed	9 / 41 (21.95%)	4 / 46 (8.70%)	
occurrences (all)	10	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	

Vomiting			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Fatty liver			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Gallstones			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Rash pruritic			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Fistula			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Infections and infestations			
Abscess on buttock			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	2	
Abscesses of skin			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Chest infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	2	0	
Cold			

subjects affected / exposed	1 / 41 (2.44%)	1 / 46 (2.17%)	
occurrences (all)	1	2	
Conjunctivitis			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Ear, nose and throat infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Flu			
subjects affected / exposed	4 / 41 (9.76%)	1 / 46 (2.17%)	
occurrences (all)	4	1	
Foot ulcer			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Unspecified suppurative otitis media			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Viral conjunctivitis			
subjects affected / exposed	1 / 41 (2.44%)	0 / 46 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 41 (0.00%)	1 / 46 (2.17%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2013	Changes requested by the Voluntary Harmonization Procedure in sections: Type / Design of the Study; Exclusion Criteria; Treatment arms and Study Treatment Procedure; Instructions for Prescribing and Performing / Taking the Study Treatment / Medication; and Safety Monitoring.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29395119