Clinical trial results:
Intravitreal Ranibizumab in pigment epithelial tears secondary to age-related macular degeneration - RIP Study

Summary

EudraCT number	2011-005807-33
Trial protocol	DE
Global end of trial date	27 January 2016

Results information

Result version number	v1 (current)
This version publication date	19 September 2021
First version publication date	19 September 2021
Summary attachment (see zip file)	Medical journal article (larsen2018-Ranibiziumab in pigment epithelial tears sencondary to age-related macular degeneration.pdf)

Trial information

Trial identification

Sponsor protocol code	Version_V3_0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01914159
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Bonn
Sponsor organisation address	Sigmund-Freud-Str. 25, Bonn, Germany, 53105
Public contact	Dr. Christoph Coch, CSSC - Studienzentrale, ccoch@uni-bonn.de
Scientific contact	Dr. Christoph Coch, CSSC - Studienzentrale, ccoch@uni-bonn.de

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	09 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 January 2016
Global end of trial reached?	Yes
Global end of trial date	27 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to investigate the effect of ranibizumab in retinal pigment epithelium tears in the presence of pigment epithelial detachments in AMD.

Protection of trial subjects:

Not applicable

Background therapy:

Not applicable

Evidence for comparator:

The efficacy of intravitreal anti-VEGF therapy in neovascular AMD has been demonstrated in various prospective large-scale clinical trials, whereby the presence of an RPE tear constituted an exclusion criterion in all of these trials. Thus, the efficacy of anti-VEGF therapy in this AMD subtype is unclear. To the best of our knowledge, the RIP study provides the first prospective efficacy data for anti-VEGF therapy in RPE tears secondary to AMD, demonstrating a stabilization of visual acuity under monthly ranibizumab therapy over 12 months.

Actual start date of recruitment	15 November 2012
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	Germany: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	0

From 65 to 84 years	23
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Study patients were recruited over a period of 26 months (02/2013 bis 04/2015) at the Departments of Ophthalmology of University of Bonn, University of Münster, and Ludwig Maximilian University Munich.

Pre-assignment

Screening details:

Only patients with neovascular activity of the AMD were included into the study. A total of 29 patients were screened for this study during the recruitment period, and 5 of these did not meet the eligibility criteria. Thus, 24 eyes of 24 patients were included in this study.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

All patients received monthly intravitreal injections of ranibizumab (0.5mg) into the study eye over the study period of 12 months. Prior to each injection, patients were examined by standardized BCVA testing according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, dilated fundus examination, spectral-domain optical coherence tomography (SD-OCT), and fundus autofluorescence imaging.

Arms

Arm title	Single-arm-trial Baseline

Arm description:

All patients received monthly intravitreal injections of ranibizumab (0.5mg) into the study eye over the study period of 12 months. Prior to each injection, patients were examined by standardized BCVA testing according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, dilated fundus examination, spectral-domain optical coherence tomography (SD-OCT), and fundus autofluorescence imaging. At baseline, additionally color fundus photography and fluorescein and indocyanine green angiography was performed to establish and document the diagnosis. Vision-related quality of life was assessed at baseline and final visit using the National Eye Institute 25 Item Visual Function Questionnaire (NEI VFQ-25).

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

Dosage and administration details:

Concentration: 10 mg/ml
Single dose: 0.5 mg
Administration: Monthly injection into the vitreous humour (intravitreal)
Duration of treatment: 12 months

Number of subjects in period 1	Single-arm-trial Baseline
Started	24
Completed	21
Not completed	3
Lost to follow-up	3

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
As there is only one treatment arm, characteristics apply to all subjects.	

Reporting group values	Baseline	Total	
Number of subjects	24	24	
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)	0	0	
From 65-84 years	23	23	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	77		
full range (min-max)	67 to 92	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	14	14	

End points

End points reporting groups

Reporting group title	Single-arm-trial Baseline

Reporting group description:

All patients received monthly intravitreal injections of ranibizumab (0.5mg) into the study eye over the study period of 12 months. Prior to each injection, patients were examined by standardized BCVA testing according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, dilated fundus examination, spectral-domain optical coherence tomography (SD-OCT), and fundus autofluorescence imaging. At baseline, additionally color fundus photography and fluorescein and indocyanine green angiography was performed to establish and document the diagnosis. Vision-related quality of life was assessed at baseline and final visit using the National Eye Institute 25 Item Visual Function Questionnaire (NEI VFQ-25).

Subject analysis set title	Final visit
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The primary endpoint is BCVA after treatment conclusion (one month after final injection) compared to baseline.

Primary: BCVA change between baseline and V13

End point title	BCVA change between baseline and V13

End point description:

End point type	Primary

End point timeframe:

The primary endpoint is BCVA after treatment conclusion (one month after final injection) compared to baseline.

End point values	Single-arm-trial Baseline	Final visit		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	24	21		
Units: ETDRS letters	24	21		

Statistical analyses

Statistical analysis title	BCVA change between baseline and V13

Statistical analysis description:

Study results were analyzed according to the intention-to–treat principle, and no last-observation-carried-forward approach was applied to drop-outs.
Mean baseline BCVA for all 24 eyes was 50.3 ETDRS letters (±18.7). Mean BCVA at final study visit was 52.9 letters (±19.7). There was no significant difference between these values (P = 0.39).

Comparison groups	Single-arm-trial Baseline v Final visit

Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.39 [2]
Method	t-test, 2-sided

Notes:

[1] - Statistical significance was assessed using paired Student’s t test, and correlation was analyzed by Pearson’s correlation coefficient. All results are expressed as means ± standard deviation.
[2] - Mean baseline BCVA for all 24 eyes was 50.3 ETDRS letters (± 18.7; Snellen equivalent 20/100; 0.69 logMAR ± 0.37). Mean BCVA at final study visit was 52.9 letters (± 19.7; Snellen equivalent 20/80; 0.64 logMAR ± 0.39).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events reporting took place from start of recruitment in 02/2013 until final visit of final patient in 01/2016.

Adverse event reporting additional description:

To assess safety data using the four eyes principle, in addition to the initial assessment of a serious adverse event by the investigator, a second assessment regarding severity, causality, and expectedness as well as a benefit-risk assessment will be undertaken by the second assessor.

Assessment type	Systematic

Dictionary used

Dictionary name	ICD
Dictionary version	10

Reporting groups

Reporting group title	Single-arm-trial

Reporting group description:

All patients received monthly intravitreal injections of ranibizumab (0.5mg) into the study eye over the study period of 12 months. Prior to each injection, patients were examined by standardized BCVA testing according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) protocol, dilated fundus examination, spectral-domain optical coherence tomography (SD-OCT), and fundus autofluorescence imaging. At baseline, additionally color fundus photography and fluorescein and indocyanine green angiography was performed to establish and document the diagnosis. Vision-related quality of life was assessed at baseline and final visit using the National Eye Institute 25 Item Visual Function Questionnaire (NEI VFQ-25).

Serious adverse events	Single-arm-trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 24 (25.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Bradicardia R00.1			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal hemorrhage H35.6			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia R13.0			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Ureteric stenosis N20.1			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Severe lumbosacral pain M54.5			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture of 3 ribs S22.3	Additional description: Horse-riding accident		
subjects affected / exposed	1 / 24 (4.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Single-arm-trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 24 (87.50%)		
Cardiac disorders			
Arterial Hypertension I10			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Cardiac arrhythmia I49.9			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Nervous system disorders			
Unspecified superficial keratitis G44.09			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Fatigue R53.83			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Other abnormality of red blood cells R71.8			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Other peripheral vertigo H81.39			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Eye disorders			
Hyposphagma H11.3			
subjects affected / exposed	8 / 24 (33.33%)		
occurrences (all)	8		
Visual Loss H53.122			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Vitreos opacities H43.399			
subjects affected / exposed	3 / 24 (12.50%)		
occurrences (all)	3		
Intraretinal fluid H35.09			
subjects affected / exposed	4 / 24 (16.67%)		
occurrences (all)	4		
Unspecified superficial keratitis H16.103			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Ocular hypertension H40.05			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Ocular pain H57.10			
subjects affected / exposed	5 / 24 (20.83%)		
occurrences (all)	5		
Viral conjunctivitis B30.9			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Retinal hemorrhage H35.6			

subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Keratoconjunctivitis sicca H16.229			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Gastrointestinal disorders			
Disease of intestine, unspecified K63.9			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Dysphagia R13. 10			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Epistaxis R04.0			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Burn of unspecified degree of forehead and cheek T20.06XA			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Unspecified skin changes R23.9			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Unspecified open wound of nose S01.20XA			
subjects affected / exposed	1 / 24 (4.17%)		
occurrences (all)	1		
Renal and urinary disorders			
Cystitis N30.00			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Infections and infestations			
Bronchitis J20.9			
subjects affected / exposed	2 / 24 (8.33%)		
occurrences (all)	2		
Acute nasopharyngitis J00			

subjects affected / exposed occurrences (all)	8 / 24 (33.33%) 8		

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30198967