



## Clinical trial results:

### Re-treatment with intravitreal application of ranibizumab guided by morphological macular changes documented by optical coherence tomography (OCT) in patients with macular edema due to branch retinal vein occlusion

#### Summary

EudraCT number	2012-005439-10
Trial protocol	DE
Global end of trial date	17 May 2016

#### Results information

Result version number	v1 (current)
This version publication date	03 January 2020
First version publication date	03 January 2020
Summary attachment (see zip file)	Synopsis (RabOCT_Ergebnisbericht_final1.0_2017-03-07_mit_Anhang.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	RabOCT
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01968239
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University of Leipzig
Sponsor organisation address	Ritterstr. 26, Leipzig, Germany, 04109
Public contact	Coordinating Investigator, Department of Ophthalmology, University of Leipzig, 0049 034197 21 650, augen@medizin.uni-leipzig.de
Scientific contact	Coordinating Investigator, Department of Ophthalmology, University of Leipzig, 0049 034197 21 650, augen@medizin.uni-leipzig.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	07 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2016
Global end of trial reached?	Yes
Global end of trial date	17 May 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This 2-armed randomized phase 2b (proof of concept) trial is primarily designed to provide first evidence on whether or not early reinjections of ranibizumab (when 1st morphologic macular changes were detected by OCT but not accompanied by BCVA loss - in contrast to current guidelines) will ensure better mid-term visual acuity in BRVO patients after 12 months of observation and treatment according to arm-specific retreatment criteria.

Primary objective is the efficacy endpoint which is the change of best corrected visual acuity (BCVA) measured in ETDRS letters.

Protection of trial subjects:

During the course of the trial, every patient was monitored closely concerning the described safety parameters. Besides the documentation of adverse events, this encompasses the following parameters at every visit:

- Increasing of IOP (intraocular pressure)
- Presence of rubeosis iridis or neovascularization in iridocorneal angle
- Presence of neovascularization of optic disk (NVDs) or retinal neovascularizations elsewhere (NVEs)

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2013
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: 18
Worldwide total number of subjects	18
EEA total number of subjects	18

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	6
From 65 to 84 years	12
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Between October 2013 and May 2015, 27 patients were screened and 18 patients were enrolled to the RabOCT study in one Trial site in Germany.

### Pre-assignment

Screening details:

The study was composed of a pre-treatment observation period and a screening phase of 1 to 7 days. Patients were enrolled to the study, if eligibility was confirmed.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	OCT group

Arm description:

OCT group (OCT guided re-treatment): Patients randomized to this group received the intravitreal injection of 0.5 mg ranibizumab if the morphological macular changes for recurrence of macular edema (microcystic changes with or without increase of central retinal thickness) was detected by OCT.

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:

0.5 mg Ranibizumab was administered if following criteria were met:

- if morphological macular changes indicating recurrence of macular edema, meaning that microcystic changes with or without increase of central retinal thickness)

In total, maximal 11 injections of Ranibizumab were applied in every study patient in the treatment period of 12 months.

<b>Arm title</b>	Control group
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Arm description:

During the entire treatment phase, the re-application of intravitreal injections (0.5 mg Ranibizumab) was administered if following criteria were met:

- if re-treatment criteria according to SmPC were fulfilled, i.e. any increase of CRT and concomitant decrease of BCVA

In total, maximal 11 injections of Ranibizumab were applied in every study patient in the treatment period of 12 months.

Arm type	Active comparator
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:

0.5 mg Ranibizumab was administered if following criteria were met:

- if re-treatment criteria according to SmPC are fulfilled, i.e. any increase of CRT and concomitant

decrease of BCVA

In total, maximal 11 injections of Ranibizumab can be applied in every study patient in the treatment period of 12 months.

<b>Number of subjects in period 1</b>	OCT group	Control group
Started	9	9
Completed	9	9

## Baseline characteristics

### Reporting groups

Reporting group title	OCT group
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Reporting group description:

OCT group (OCT guided re-treatment): Patients randomized to this group received the intravitreal injection of 0.5 mg ranibizumab if the morphological macular changes for recurrence of macular edema (microcystic changes with or without increase of central retinal thickness) was detected by OCT.

Reporting group title	Control group
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Reporting group description:

During the entire treatment phase, the re-application of intravitreal injections (0.5 mg Ranibizumab) was administered if following criteria were met:

- if re-treatment criteria according to SmPC were fulfilled, i.e. any increase of CRT and concomitant decrease of BCVA

In total, maximal 11 injections of Ranibizumab were applied in every study patient in the treatment period of 12 months.

Reporting group values	OCT group	Control group	Total
Number of subjects	9	9	18
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	3	6
From 65-84 years	6	6	12
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	68.6	69.1	-
standard deviation	± 6.8	± 8.2	-
Gender categorical			
Units: Subjects			
Female	7	5	12
Male	2	4	6
neovascularization			
neovascularization from ophthalmoscopy/biomicroscopy			
Units: Subjects			
No	9	9	18
Yes	0	0	0
microcysts			
microcysts present from OCT			
Units: Subjects			
No	0	1	1
Yes	9	8	17

Study eye			
Study eye			
Units: Subjects			
right	4	6	10
left	5	3	8
Body-Max-Index			
Body-Max-Index			
Units: kg/m2			
arithmetic mean	28.5	30.0	
standard deviation	± 5.3	± 5.4	-
BCVA of study eye			
BCVA of study eye			
Units: Letters			
arithmetic mean	75.7	72.9	
standard deviation	± 5.9	± 11.4	-
CRT of study eye			
CRT of study eye			
Units: µm			
arithmetic mean	283.3	310.8	
standard deviation	± 79.0	± 162.6	-
intra ocular pressure of study eye			
intra ocular pressure of study eye			
Units: mm Hg			
arithmetic mean	15.2	15.9	
standard deviation	± 2.0	± 2.6	-

## End points

### End points reporting groups

Reporting group title	OCT group
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Reporting group description:

OCT group (OCT guided re-treatment): Patients randomized to this group received the intravitreal injection of 0.5 mg ranibizumab if the morphological macular changes for recurrence of macular edema (microcystic changes with or without increase of central retinal thickness) was detected by OCT.

Reporting group title	Control group
-----------------------	---------------

Reporting group description:

During the entire treatment phase, the re-application of intravitreal injections (0.5 mg Ranibizumab) was administered if following criteria were met:

- if re-treatment criteria according to SmPC were fulfilled, i.e. any increase of CRT and concomitant decrease of BCVA

In total, maximal 11 injections of Ranibizumab were applied in every study patient in the treatment period of 12 months.

### Primary: Change of BCVA

End point title	Change of BCVA
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End point description:

Based on the BCVA assessment of the study eye - performed at all study visits and measured in ETDRS letters - the primary end point was the change score in BCVA from randomization (week 1) to week 52, i.e. end of study (EoS)

End point type	Primary
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End point timeframe:

from randomization (week 1) to week 52, i.e. end of study (EoS)

End point values	OCT group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: letters				
arithmetic mean (standard deviation)	4.3 ( $\pm$ 6.1)	6.8 ( $\pm$ 10.6)		

### Statistical analyses

Statistical analysis title	Estimation of the between-groups mean
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Statistical analysis description:

Estimation of the between-groups mean difference with the corresponding 95% confidence interval

Comparison groups	Control group v OCT group
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Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0.349 <sup>[2]</sup>
Method	repeated-measures ANCOVA of BCVA change
Parameter estimate	mean difference in change
Point estimate	-2.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.06
upper limit	6.17

Notes:

[1] - Data description/ estimation of group difference with confidence interval

[2] - expoloratory due to small sample size

### Secondary: Change in CRT

End point title	Change in CRT
End point description:	
Change score in central retinal thickness (CRT), assessed by OCT between Week 1 and week 52 (EoS)	
End point type	Secondary
End point timeframe:	
Between Week 1 and week 52 (EoS)	

End point values	OCT group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: µm				
arithmetic mean (standard deviation)	-42.4 (± 76.9)	-80.8 (± 164.4)		

### Statistical analyses

Statistical analysis title	Estimation of the between-groups mean
Statistical analysis description:	
Estimation of the between-groups mean difference with the corresponding 95% confidence interval for the secondary endpoint	
Comparison groups	OCT group v Control group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 0.23 <sup>[4]</sup>
Method	repeated-measures ANCOVA of CRT change
Parameter estimate	mean difference in change
Point estimate	38.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-94.35
upper limit	171.01

Notes:

[3] - data description/ estimation of group difference with confidence interval

[4] - expoloratory due to small sample size

## Secondary: Number of indicated Ranibizumab injections

End point title	Number of indicated Ranibizumab injections
End point description: The number of indicated Ranibizumab injections in the two groups until last FU visit was compared by Mann-Whitney-U-Test	
End point type	Secondary
End point timeframe: 52 week	

End point values	OCT group	Control group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	9		
Units: Number of injections				
median (inter-quartile range (Q1-Q3))	9 (7 to 12.5)	8 (4.5 to 9)		

## Statistical analyses

Statistical analysis title	Number of indicated Ranibizumab injections
Statistical analysis description: The number of indicated Ranibizumab injections in the two groups until last FU visit was compared by Mann-Whitney-U-Test	
Comparison groups	Control group v OCT group
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
P-value	= 0.258 <sup>[6]</sup>
Method	Mann-Whitney U test
Parameter estimate	Median difference and Hodges-Lehman st.
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	5

Notes:

[5] - data description/ estimation of group difference with confidence interval

[6] - expoloratory due to small sample size

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were documented from randomization up to 30 days after the last study intervention or the termination visit, whichever was later.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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### Reporting groups

Reporting group title	OCT group
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Reporting group description: -

Reporting group title	Control group
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Reporting group description: -

Serious adverse events	OCT group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	1 / 9 (11.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Biopsy bladder			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
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			
Bronchiectasis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (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 %

<b>Non-serious adverse events</b>	OCT group	Control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	3 / 9 (33.33%)	
Investigations			
Intraocular pressure increased	Additional description: possibly injection procedure-related AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Injection site pain	Additional description: possibly injection procedure-related AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	
Eye disorders			
Vitreous detachment	Additional description: possibly injection procedure-related AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	1	0	
Eye pain	Additional description: possibly injection procedure-related AE		
subjects affected / exposed	1 / 9 (11.11%)	0 / 9 (0.00%)	
occurrences (all)	2	0	
Conjunctival haemorrhage	Additional description: possibly injection procedure-related AE		
subjects affected / exposed	1 / 9 (11.11%)	2 / 9 (22.22%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea	Additional description: possibly injection procedure-related AE		
subjects affected / exposed	0 / 9 (0.00%)	1 / 9 (11.11%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2013	Change of Coordinating Investigator and Authorised Representative of the Sponsor. PD Dr. habil. Matus Rehak left the Department of Ophthalmology of the University of Leipzig on January 2014. Therefore Prof. Dr. med. Peter Wiedemann took over the responsibilities of the coordinating investigator as well as of the authorised representative of the sponsor. Furthermore, some corrections and clarifications were described.
03 December 2015	Change in number of recruited patients and prolongation of trial duration and stop of recruitment phase. The recruitment of patients was low and although the recruitment phase was prolonged, 18 instead of 24 patients were allocated to the study up to May 2015. Therefore, it was decided to stop the recruitment of further patients. All patients enrolled up to this time point completed the trial according to the protocol. The statistical analyses were performed with these 18 patients.

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported