



## Clinical trial results:

### Treatment of macular edema due to central retinal vein occlusion with ranibizumab (Lucentis®).

#### Summary

EudraCT number	2009-017782-30
Trial protocol	AT
Global end of trial date	15 June 2016

#### Results information

Result version number	v1 (current)
This version publication date	20 December 2018
First version publication date	20 December 2018
Summary attachment (see zip file)	Summary attachment (Abschlussbericht 2017.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	Lucentis in CRVO
-----------------------	------------------

##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Medizinische Universität Graz
Sponsor organisation address	Auenbruggerplatz 4, Graz, Austria, 8036
Public contact	Weger, Martin, Ao.Univ.-Prof. Dr.med.univ., Medizinische Universität Graz, 0043 385-14086, martin.weger@medunigraz.at
Scientific contact	Weger, Martin, Ao.Univ.-Prof. Dr.med.univ., Medizinische Universität Graz, 0043 385-14086, martin.weger@medunigraz.at

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	13 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 June 2016
Global end of trial reached?	Yes
Global end of trial date	15 June 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Explore whether intravitreal ranibizumab is an effective, safe and convenient treatment for patients with macular edema due to central retinal vein occlusion. Aim of the study is to increase the visual acuity by 15 EDTRS letters in 50% of the patients.

Protection of trial subjects:

Measures taken to minimize the risk of potential adverse events associated with serial intraocular injections included e.g. aseptic technique, anesthesia, drug preparation and administration.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	12
From 65 to 84 years	8

85 years and over	0
-------------------	---

## Subject disposition

### Recruitment

Recruitment details:

The recruitment target as defined in the protocol was achieved (20 patients).

### Pre-assignment

Screening details:

There have been no screening failures in the course of the study.

### Period 1

Period 1 title	Baseline to first injection
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

<b>Arm title</b>	intravitreal ranibizumab injections
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ranibizumamb
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Enrolled patients received one intravitreal injection of 0.5 mg ranibizumab (month 0). At month 1 and 2 patients received an additional intravitreal injection of 0.5 mg ranibizumab. Follow-up was performed at a monthly basis for a total of 12 months. After month 2 additional ranibizumab injections have been administered, if there was (1) a loss of 5 EDTRS letters accompanied by fluid in the macula as detected by OCT, or (2) persistent macular edema, or (3) an increase in central retinal thickness as detected by OCT. During the 12-month study period a maximum of 12 intravitreal ranibizumab injections were administered.

<b>Number of subjects in period 1</b>	intravitreal ranibizumab injections
Started	20
Completed	20

### Period 2

Period 2 title	First injection to complete follow-up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

<b>Arm title</b>	intravitreal ranibizumab injections
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Ranibizumamb
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

### Dosage and administration details:

Enrolled patients received one intravitreal injection of 0.5 mg ranibizumab (month 0). At month 1 and 2 patients received an additional intravitreal injection of 0.5 mg ranibizumab. Follow-up was performed at a monthly basis for a total of 12 months. After month 2 additional ranibizumab injections have been administered, if there was (1) a loss of 5 EDTRS letters accompanied by fluid in the macula as detected by OCT, or (2) persistent macular edema, or (3) an increase in central retinal thickness as detected by OCT. During the 12-month study period a maximum of 12 intravitreal ranibizumab injections were administered.

<b>Number of subjects in period 2</b>	intravitreal ranibizumab injections
Started	20
Completed	19
Not completed	1
Consent withdrawn by subject	1

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline to first injection
Reporting group description: -	

Reporting group values	Baseline to first injection	Total	
Number of subjects	20	20	
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	0	0	
85 years and over	0	0	
30-45 years	2	2	
46-55 years	3	3	
56-65 years	7	7	
66-75 years	2	2	
76-85	6	6	
Gender categorical Units: Subjects			
Female	9	9	
Male	11	11	

### Subject analysis sets

Subject analysis set title	Baseline
Subject analysis set type	Per protocol

Subject analysis set description:

For the quantitative analysis, only patients with complete follow-up were included. Patients with incomplete follow-up and screening failure were excluded.

Subject analysis set title	End data- patients after complete follow-up
Subject analysis set type	Per protocol

Subject analysis set description:

For the quantitative analysis, only patients with complete follow-up were included. Patients with incomplete follow-up and screening failure were excluded.

Reporting group values	Baseline	End data- patients after complete follow-up	
Number of subjects	20	19	

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	0	0	
85 years and over	0	0	
30-45 years	2	2	
46-55 years	3	3	
56-65 years	7	7	
66-75 years	2	2	
76-85	5	4	
Gender categorical			
Units: Subjects			
Female	9	8	
Male	11	11	

## End points

### End points reporting groups

Reporting group title	intravitreal ranibizumab injections
Reporting group description: -	
Reporting group title	intravitreal ranibizumab injections
Reporting group description: -	
Subject analysis set title	Baseline
Subject analysis set type	Per protocol
Subject analysis set description:	
For the quantitative analysis, only patients with complete follow-up were included. Patients with incomplete follow-up and screening failure were excluded.	
Subject analysis set title	End data- patients after complete follow-up
Subject analysis set type	Per protocol
Subject analysis set description:	
For the quantitative analysis, only patients with complete follow-up were included. Patients with incomplete follow-up and screening failure were excluded.	

### Primary: Efficacy - increase of visual acuity by 15 EDTRS letters

End point title	Efficacy - increase of visual acuity by 15 EDTRS letters
End point description:	
Fifteen of the 19 patients (79%) gained 15 EDTRS letters or more after intravitreal injections of ranibizumab after twelve months	
End point type	Primary
End point timeframe:	
12 months after first treatment	

End point values	intravitreal ranibizumab injections	Baseline	End data- patients after complete follow-up	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20 <sup>[1]</sup>	20 <sup>[2]</sup>	19 <sup>[3]</sup>	
Units: letters	20	20	19	

Notes:

[1] - 20 patients received intravitreal ranibizumab injections

[2] - 20

[3] - 19

### Statistical analyses

Statistical analysis title	Efficacy
Comparison groups	Baseline v End data- patients after complete follow-up
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority <sup>[4]</sup>
P-value	≤ 5
Method	t-test, 2-sided



Notes:

[4] - All statistical analyses have been performed using STATA 13 (StataCorp LP, USA).

Mean changes were evaluated using spearman's correlation and t-test. P-values of 0.05 were considered significant.

### Secondary: Proportion of patients who gain 15 letters of BCVA

End point title	Proportion of patients who gain 15 letters of BCVA
End point description: Fifteen of the 19 patients (63%) gained 15 letters of BCVA or more after intravitreal injections of ranibizumab using a pro re nata approach after six months.	
End point type	Secondary
End point timeframe: 6 months	

End point values	Baseline	End data- patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: letters	20	19		

### Statistical analyses

No statistical analyses for this end point

### Secondary: patients who lose less than 15 letters of BCVA

End point title	patients who lose less than 15 letters of BCVA
End point description: 17 of the 19 patients (89%) lost less than 15 letters of BCVA from baseline at month 6 and all patients (100%) lost less than 15 letters of BCVA at month 12.	
End point type	Secondary
End point timeframe: 6 and 12 months after first treatment	

End point values	Baseline	End data- patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: letters	20	19		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change in central retinal thickness

End point title	Mean change in central retinal thickness
-----------------	--

End point description:

Mean central retinal thickness decreased from 701µm at baseline to 389µm at month 6 (p<0.01) and to 348µm at month 12 (p<0.01).

End point type	Secondary
----------------	-----------

End point timeframe:

Month 6, Month 12 after first treatment

End point values	Baseline	End data-patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: µm				
number (not applicable)	20	19		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change in contrast sensitivity

End point title	Mean change in contrast sensitivity
-----------------	-------------------------------------

End point description:

Contrast sensitivity increased in the study eye from 0.91 at baseline to 1.33 at month 6 (p<0.01) and 1.41 at month 12 (p<0.01) .

End point type	Secondary
----------------	-----------

End point timeframe:

Months 6 and 12 after first treatment

End point values	Baseline	End data-patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: letters	20	19		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean number of ranibizumab injections needed for resolution of macular edema

End point title	Mean number of ranibizumab injections needed for resolution of macular edema
-----------------	--

End point description:

Patients received on average 7.2 injections (SD 3.1) within one-year. Seventeen of the 19 patients showed complete resolution

End point type	Secondary
----------------	-----------

End point timeframe:

12 months after first treatment

End point values	Baseline	End data-patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: Number of injections	20	19		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean number in reading speed

End point title	Mean number in reading speed
-----------------	------------------------------

End point description:

Reading speed increased in the study eye from 39.3 wpm (words per minute) at baseline to 77 wpm at month 6 ( $p < 0.01$ ) and 88.4 wpm at month 12 ( $p < 0.01$ ) .

End point type	Secondary
----------------	-----------

End point timeframe:

Months 6 and 12 after first treatment

End point values	Baseline	End data-patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: number of words per minute	20	19		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change in arterio-venous passage time

End point title	Mean change in arterio-venous passage time
-----------------	--

End point description:

Due to impaired assessability of the fluorescein angiography images this secondary variable was not analysed

End point type	Secondary
----------------	-----------

End point timeframe:

6 and 12 month from baseline

End point values	Baseline	End data- patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: seconds	20	19		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change in quality of life scores

End point title	Mean change in quality of life scores
-----------------	---------------------------------------

End point description:

Mean NEI VFQ-25 score improved from 82.4 at baseline to 92.5 at month 6 ( $p < 0.01$ ) and 94.8 at month 12 ( $p < 0.01$ ).

End point type	Secondary
----------------	-----------

End point timeframe:

6 and 12 month compared to baseline

End point values	intravitreal ranibizumab injections	Baseline	End data- patients after complete follow-up	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	19 <sup>[5]</sup>	20 <sup>[6]</sup>	19 <sup>[7]</sup>	
Units: score	19	20	19	

Notes:

[5] - patients with complete Follow-up

[6] - 20

[7] - 19

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Change from baseline in best corrected visual acuity (BCVA) at months 6

End point title	Mean Change from baseline in best corrected visual acuity (BCVA) at months 6
End point description: Mean change from baseline in BCVA was +20 letters at month 6 ( $p < 0.01$ )	
End point type	Secondary
End point timeframe: 6 months after baseline	

End point values	Baseline	End data-patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: letters	20	19		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean Change from baseline in best corrected visual acuity (BCVA) at months 12

End point title	Mean Change from baseline in best corrected visual acuity (BCVA) at months 12
End point description: Mean change from baseline in BCVA was +23 at month 12 ( $p < 0.01$ ).	
End point type	Secondary
End point timeframe: 12 months after baseline	

End point values	Baseline	End data-patients after complete follow-up		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed				
Units: letters	20	19		

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Informed Consent to 12 months after first Administration of study treatment

Assessment type	Non-systematic
-----------------	----------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20,0
--------------------	------

### Reporting groups

Reporting group title	Patients who signed Informed Consent
-----------------------	--------------------------------------

Reporting group description: -

Serious adverse events	Patients who signed Informed Consent		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Patients who signed Informed Consent		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)		
General disorders and administration site conditions			
Vertigo			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
hematoma			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			

Intraocular pressure increased subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
floaters in eye subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Corneal erosion subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Meibomian gland dysfunction subjects affected / exposed occurrences (all)	2 / 20 (10.00%) 2		
Infections and infestations Fever blister subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 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**

None reported