



Clinical trial results:

Anti-VEGF (bevacizumab/ranibizumab) versus RPE-choroid graft in the treatment of 1) non-responders to 3 intravitreal anti-VEGF injections, or 2) patients with AMD and pigment epithelium rip, or 3) patients with AMD and massive haemorrhage. A randomized trial.

Summary

EudraCT number	2008-008259-41
Trial protocol	NL
Global end of trial date	26 August 2011

Results information

Result version number	v1
This version publication date	01 February 2016
First version publication date	11 February 2015

Trial information

Trial identification

Sponsor protocol code	OZR-2008-20
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trial Register: NTR1768

Notes:

Sponsors

Sponsor organisation name	The Rotterdam Eye Hospital
Sponsor organisation address	PO Box 70030, Rotterdam, Netherlands, 3000LM
Public contact	Rotterdam Ophthalmic Institute, The Rotterdam Eye Hospital, +31 10 4023449, roi@oogziekenhuis.nl
Scientific contact	Rotterdam Ophthalmic Institute, The Rotterdam Eye Hospital, +31 10 4023449, roi@oogziekenhuis.nl

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	10 February 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2011
Global end of trial reached?	Yes
Global end of trial date	26 August 2011
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare visual outcome (distance and reading) and foveal fixation (biomicroscopy, microperimetry) of RPE-choroid graft translocation versus intravitreal anti-VEGF therapy at 12 and 24 months.

Protection of trial subjects:

No specific measures.

Background therapy:

Standard treatment for patients with exudative age-related macular degeneration (AMD) is intravitreal injection of anti-VEGF. Because alternatives are not available, at present, also those patients for whom this therapy probably does not help to improve prospects are initially treated with anti-VEGF. Recently, however, it has been shown that a retinal pigment epithelium (RPE)-choroid graft translocation in the treatment of patients with choroidal neovascular lesions of AMD can stabilize or even improve visual acuity.

In this study, it will be investigated whether RPE-choroid graft translocation provides a better alternative to anti-VEGF medication for AMD patients for whom prospects are rather poor otherwise.

Evidence for comparator: -

Actual start date of recruitment	06 October 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 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)	1
From 65 to 84 years	10
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

Patients with exudative subfoveal AMD in combination with either of the following conditions:

- 1) visual loss of 15 letters on the ETDRS chart after 3 anti-VEGF injections,
- 2) subfoveal RPE-tear,
- 3) massive submacular haemorrhage.

Pre-assignment

Screening details:

All patients from subgroup 3 will have their submacular haemorrhage surgically removed irrespective of the study arm they are assigned to.

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
Arm title	Graft translocation.

Arm description:

Retinal pigment epithelium - choroid translocation (from periphery to macular region).

Arm type	Experimental
Investigational medicinal product name	No product (intervention is surgical procedure).
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Living tissue equivalent
Routes of administration	Other use

Dosage and administration details:

None (intervention is surgical procedure).

Arm title	Anti-VEGF.
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Arm description:

Continued intravitreal anti-VEGF injections.

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab.
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin.
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravitreal use

Dosage and administration details:

1.25 mg bevacizumab (0.05 ml) injections based on PrONTO protocol (Am J Ophthalmol, 2007; 143:566).

Number of subjects in period 1	Graft translocation.	Anti-VEGF.
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups

Reporting group title	Graft translocation.
Reporting group description:	
Retinal pigment epithelium - choroid translocation (from periphery to macular region).	
Reporting group title	Anti-VEGF.
Reporting group description:	
Continued intravitreal anti-VEGF injections.	

Reporting group values	Graft translocation.	Anti-VEGF.	Total
Number of subjects	10	10	20
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	78.6	83.8	
standard deviation	± 10.4	± 8.2	-
Gender categorical Units: Subjects			
Female	8	5	13
Male	2	5	7

End points

End points reporting groups

Reporting group title	Graft translocation.
Reporting group description: Retinal pigment epithelium - choroid translocation (from periphery to macular region).	
Reporting group title	Anti-VEGF.
Reporting group description: Continued intravitreal anti-VEGF injections.	

Primary: Visual acuity

End point title	Visual acuity
End point description:	
End point type	Primary
End point timeframe: 12 months post-op (LOCF).	

End point values	Graft translocation.	Anti-VEGF.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: LogMAR				
arithmetic mean (standard deviation)	0.4 (\pm 0.7)	0.2 (\pm 0.4)		

Statistical analyses

Statistical analysis title	Visual acuity change.
Comparison groups	Graft translocation. v Anti-VEGF.
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months post-op.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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Reporting groups

Reporting group title	Graft translocation.
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Reporting group description:

Retinal pigment epithelium - choroid translocation (from periphery to macular region).

Reporting group title	Anti-VEGF.
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Reporting group description:

Continued intravitreal anti-VEGF injections.

Serious adverse events	Graft translocation.	Anti-VEGF.	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Graft translocation.	Anti-VEGF.	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	1 / 10 (10.00%)	
Eye disorders			

Proliferative vitreoretinopathy subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	1 / 10 (10.00%) 1	
Submacular hemorrhage (recurrent) subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 3	0 / 10 (0.00%) 0	
Hypotension (ocular) subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2	0 / 10 (0.00%) 0	

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? Yes

Date	Interruption	Restart date
26 August 2011	The multicenter study was stopped because inclusion failed in other centers. The included patient group is far too small to draw conclusions whether an RPE-choroid graft or anti-VEGF treatment is more successful. Also, this surgical group suffered an unprecedented run of complications. Both gain and loss of VA may be experienced by patients undergoing either treatment method; more gain might be possible for patients with a graft, however, in the absence of complications.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

See, van Zeeburg EJT, Thesis 2014: Chapt. 4.1.

http://repub.eur.nl/pub/50334/140115_Zeeburg-Elsbeth-Janneke-Theodora-van_Part1.pdf

Notes: