



## Clinical trial results: Avastin-Injections in Age Related Macular Degeneration: Prospective Study for Optimal Frequency and Follow-up Determination

Due to a system error, the data reported in v1 and v2 are not correct and have been removed from public view.

### Summary

EudraCT number	2007-003766-17
Trial protocol	NL
Global end of trial date	27 May 2013

### Results information

Result version number	v3
This version publication date	31 January 2016
First version publication date	25 December 2014
Version creation reason	• Correction of full data set Correction adverse events.

### Trial information

#### Trial identification

Sponsor protocol code	2007-06
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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: NTR1174

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	03 June 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 May 2013
Global end of trial reached?	Yes
Global end of trial date	27 May 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To determine the optimal Avastin injection schedule.

Protection of trial subjects:

No specific measures.

Background therapy:

Age-related macular degeneration (ARMD) results in a deterioration of the central retinal function, and is the leading cause of blindness in people over 50 years of age in Europe and the USA. The wet form of ARMD, with choroidal neovascularization, is more aggressive and may progress more rapidly to blindness. Recently, Lucentis® has been registered for treatment of wet ARMD, but is (as yet) not reimbursed by health care insurance. Avastin® appears to be a cost-effective alternative for Lucentis®, but an optimal injection schedule has not been determined so far. A reduction of the number of injections, without loss of treatment efficacy, would have a number of beneficial effects: a decrease of the risk associated with intravitreal injection (such as endophthalmitis), cost-effectiveness and reduced ophthalmic work-load.

Evidence for comparator: -

Actual start date of recruitment	03 June 2008
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: 311
Worldwide total number of subjects	311
EEA total number of subjects	311

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	246
85 years and over	65

## Subject disposition

### Recruitment

Recruitment details:

Patients with exudative ARMD.

### Pre-assignment

Screening details:

Use of coumarin-derivatives at the time of inclusion.

Clinical significant CVA or MCI in the 6 months prior to planned inclusion.

### 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>	Every 4 weeks

Arm description:

Avastin injection every 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

1.25 mg (in 0.05 ml) every 4 weeks.

<b>Arm title</b>	Every 6 weeks.
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Arm description:

Avastin injection every 6 weeks

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

1.25 mg (in 0.05 ml) every 6 weeks.

<b>Arm title</b>	Every 8 weeks.
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Arm description:

Avastin injection every 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:  
1.25 mg (in 0.05 ml) every 8 weeks.

<b>Arm title</b>	Visit every 4 weeks.
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Arm description:

Visit every 4 weeks, Avastin injection on demand.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

1.25 mg (in 0.05 ml) on demand.

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Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	EU/1/04/300/001
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

1.25 mg (in 0.05 ml) on demand.

<b>Number of subjects in period 1</b>	Every 4 weeks	Every 6 weeks.	Every 8 weeks.
Started	64	63	64
Completed	46	57	54
Not completed	18	6	10
Lost to follow-up	18	6	10

<b>Number of subjects in period 1</b>	Visit every 4 weeks.	Visit every 8 weeks.
Started	60	60
Completed	51	57
Not completed	9	3
Lost to follow-up	9	3

## Baseline characteristics

### Reporting groups

Reporting group title	Every 4 weeks
Reporting group description: Avastin injection every 4 weeks.	
Reporting group title	Every 6 weeks.
Reporting group description: Avastin injection every 6 weeks	
Reporting group title	Every 8 weeks.
Reporting group description: Avastin injection every 8 weeks.	
Reporting group title	Visit every 4 weeks.
Reporting group description: Visit every 4 weeks, Avastin injection on demand.	
Reporting group title	Visit every 8 weeks.
Reporting group description: Visit every 8 weeks, Avastin injection on demand.	

Reporting group values	Every 4 weeks	Every 6 weeks.	Every 8 weeks.
Number of subjects	64	63	64
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	77.7	78.6	79.4
standard deviation	± 6.8	± 6.5	± 6.2
Gender categorical Units: Subjects			
Female	46	38	43
Male	18	25	21

Reporting group values	Visit every 4 weeks.	Visit every 8 weeks.	Total
Number of subjects	60	60	311
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	77.6	79.1	
standard deviation	± 6.8	± 7.2	-
Gender categorical			
Units: Subjects			
Female	36	38	201
Male	24	22	110

## End points

### End points reporting groups

Reporting group title	Every 4 weeks
Reporting group description: Avastin injection every 4 weeks.	
Reporting group title	Every 6 weeks.
Reporting group description: Avastin injection every 6 weeks	
Reporting group title	Every 8 weeks.
Reporting group description: Avastin injection every 8 weeks.	
Reporting group title	Visit every 4 weeks.
Reporting group description: Visit every 4 weeks, Avastin injection on demand.	
Reporting group title	Visit every 8 weeks.
Reporting group description: Visit every 8 weeks, Avastin injection on demand.	

### Primary: Visual acuity.

End point title	Visual acuity.
End point description:	
End point type	Primary
End point timeframe: At 1 year.	

End point values	Every 4 weeks	Every 6 weeks.	Every 8 weeks.	Visit every 4 weeks.
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	57	54	51
Units: Letters gained (ETDRS chart).				
arithmetic mean (standard deviation)	1.9 ( $\pm$ 13.8)	1.6 ( $\pm$ 11)	6 ( $\pm$ 8.9)	5.6 ( $\pm$ 10.2)

End point values	Visit every 8 weeks.			
Subject group type	Reporting group			
Number of subjects analysed	57			
Units: Letters gained (ETDRS chart).				
arithmetic mean (standard deviation)	4.6 ( $\pm$ 12)			



## Statistical analyses

<b>Statistical analysis title</b>	VA gain.
Comparison groups	Every 4 weeks v Every 6 weeks. v Every 8 weeks. v Visit every 4 weeks. v Visit every 8 weeks.
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

One year follow up.

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	Every 4 weeks.
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Reporting group description: -

Reporting group title	Every 6 weeks.
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Reporting group description: -

Reporting group title	Every 8 weeks.
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Reporting group description: -

Reporting group title	Visit every 4 weeks, injection on demand.
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Reporting group description: -

Reporting group title	Visit every 8 weeks, injection on demand.
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Reporting group description: -

<b>Serious adverse events</b>	Every 4 weeks.	Every 6 weeks.	Every 8 weeks.
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 64 (14.06%)	4 / 63 (6.35%)	9 / 64 (14.06%)
number of deaths (all causes)	2	1	0
number of deaths resulting from adverse events			
Vascular disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 64 (1.56%)	1 / 63 (1.59%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	2 / 64 (3.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			

subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
<b>Blood and lymphatic system disorders</b>			
Atherothrombotic event.			
subjects affected / exposed	2 / 64 (3.13%)	1 / 63 (1.59%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
<b>Eye disorders</b>			
Retinal pigment epithelial tear			
subjects affected / exposed	2 / 64 (3.13%)	2 / 63 (3.17%)	4 / 64 (6.25%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis or pseudoendophthalmitis			
subjects affected / exposed	2 / 64 (3.13%)	0 / 63 (0.00%)	0 / 64 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other ocular event.			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	1 / 64 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Visit every 4 weeks, injection on demand.	Visit every 8 weeks, injection on demand.	
<b>Total subjects affected by serious adverse events</b>			
subjects affected / exposed	3 / 60 (5.00%)	2 / 60 (3.33%)	
number of deaths (all causes)	3	0	
number of deaths resulting from adverse events			
<b>Vascular disorders</b>			
Cerebrovascular accident			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	3 / 60 (5.00%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Blood and lymphatic system disorders			
Atherothrombotic event.			
subjects affected / exposed	1 / 60 (1.67%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal pigment epithelial tear			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis or pseudoendophthalmitis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 60 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Other ocular event.			
subjects affected / exposed	1 / 60 (1.67%)	1 / 60 (1.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Every 4 weeks.	Every 6 weeks.	Every 8 weeks.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 64 (0.00%)	0 / 63 (0.00%)	0 / 64 (0.00%)
Eye disorders			

Vitreous hemorrhage subjects affected / exposed occurrences (all)	0 / 64 (0.00%) 0	0 / 63 (0.00%) 0	0 / 64 (0.00%) 0
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<b>Non-serious adverse events</b>	Visit every 4 weeks, injection on demand.	Visit every 8 weeks, injection on demand.	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
Eye disorders			
Vitreous hemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	1 / 60 (1.67%)	
occurrences (all)	0	1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23773796>