Clinical trial results:
Intravitreal versus submacular injection of rtPA for acute submacular haemorrhages.

Summary

EudraCT number	2010-023636-17
Trial protocol	NL
Global end of trial date	19 March 2014

Results information

Result version number	v2 (current)
This version publication date	30 March 2016
First version publication date	18 March 2015
Version creation reason	• New data added to full data set Addition of online reference.

Trial information

Trial identification

Sponsor protocol code	OZR-2010-22

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trial Register: NTR3359

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	30 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2014
Global end of trial reached?	Yes
Global end of trial date	19 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To examine which route of rtPA administration (submacular or intravitreal) is most effective with respect to dislocation and/or volume reduction of SMH at 3 months.

Protection of trial subjects:

None specified.

Background therapy:

Submacular haemorrhage (SMH) is a severe complication of age-related macular degeneration (AMD). If untreated, the SMH itself will cause irreversible damage to the retina and retinal pigment epithelium (RPE). Recombinant tissue plasminogen activator (rtPA) is a fibrolytic enzyme which can liquefy blood clots by converting plasminogen into active plasmin, which is needed for the breakdown of fibrin.Two treatment modalities of SMH have been compared.

Evidence for comparator:

In this study, the investigational topic was the route of administration of rtPA: submacular (Arm 1) and intravitreal (Arm 2).

Actual start date of recruitment	13 September 2013
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: 25
Worldwide total number of subjects	25
EEA total number of subjects	25

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	19
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Consecutive patients with SMH existing ≤ 14 days at time of surgery.

Pre-assignment

Screening details:

INR.

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	Submacular rtPA

Arm description:

Submacular injection of rtPA with pars plana vitrectomy.

Arm type	Active comparator
Investigational medicinal product name	alteplase
Investigational medicinal product code	RVG 103374
Other name	Actilyse Cathflo®
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Ophthalmic use

Dosage and administration details:

Submacular injection: 0.1 ml; 25 µg rtPA.

Arm title	Intravitreal rtPA.

Arm description:

Intravitreal injection of rtPA.

Arm type	Experimental
Investigational medicinal product name	alteplase
Investigational medicinal product code	RVG 103374
Other name	Actilyse Cathflo®
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Ophthalmic use

Dosage and administration details:

Intravitreal injection: 0.1 ml; 25 µg rtPA.

Number of subjects in period 1	Submacular rtPA	Intravitreal rtPA.
Started	13	12
Completed	11	11
Not completed	2	1
Adverse event, non-fatal	1	1
retinal macroaneurysms	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Submacular rtPA
Reporting group description:	
Submacular injection of rtPA with pars plana vitrectomy.	
Reporting group title	Intravitreal rtPA.
Reporting group description:	
Intravitreal injection of rtPA.	

Reporting group values	Submacular rtPA	Intravitreal rtPA.	Total
Number of subjects	13	12	25
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)	0	0	0
From 65-84 years	10	9	19
85 years and over	3	3	6
Age continuous Units: years			
arithmetic mean	79.1	81.8	
standard deviation	± 8.6	± 5.1	-
Gender categorical Units: Subjects			
Female	7	8	15
Male	6	4	10

End points

End points reporting groups

Reporting group title	Submacular rtPA
Reporting group description:	
Submacular injection of rtPA with pars plana vitrectomy.	
Reporting group title	Intravitreal rtPA.
Reporting group description:	
Intravitreal injection of rtPA.	

Primary: Volume reduction.

End point title	Volume reduction.[1]
End point description:	
End point type	Primary
End point timeframe:	
SMH volume reduction at 6 weeks.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was intended as a pilot study and, therefore, is not adequately powered for statistical comparison.

End point values	Submacular rtPA	Intravitreal rtPA.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	11		
Units: Proportion				
arithmetic mean (standard deviation)	0.92 (± 0.13)	0.91 (± 0.13)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Until 12 months after rtPA injection.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	Submacular rtPA.
Reporting group description: -	
Reporting group title	Intravitreal rtPA.
Reporting group description: -	

Serious adverse events	Submacular rtPA.	Intravitreal rtPA.	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	1 / 12 (8.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Arrhythmia	Additional description: Patient had history of arrhythmia; on this occasion hospitalized.		
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope	Additional description: Patient had history of syncope; on this occasion hospitalized.		
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia	Additional description: Patient was hospitalized.		
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (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: 5 %

Non-serious adverse events	Submacular rtPA.	Intravitreal rtPA.	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)	4 / 12 (33.33%)	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Retinal vascular occlusion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Retinal pigment epithelial tear			
subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	2 / 12 (16.67%)	
occurrences (all)	0	2	
Macular hole			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Cataract			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Subretinal haematoma	Additional description: Recurrent.		
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	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? No

Limitations and caveats

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

Submacular injection of rtPA was performed in combination with pars plana vitrectomy and was, therefore, a more invasive procedure than intravitreal injection of rtPA. It may involve a higher risk of complications.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/26807631