



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 | v1 |
| This version publication date | 01 February 2016 |
| First version publication date | 18 March 2015 |

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

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|-----------------|--------|
| 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.

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| 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. |
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Notes: