



## Clinical trial results:

**Does oral administration of dabigatran etexilate, a direct thrombin inhibitor, achieve clinical significant concentrations of dabigatran and thrombin inhibiting activity in vitreous and subretinal fluid?**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-000388-41 |
| Trial protocol           | NL             |
| Global end of trial date | 22 April 2015  |

### Results information

|                                |                                                          |
|--------------------------------|----------------------------------------------------------|
| Result version number          | v2 (current)                                             |
| This version publication date  | 27 July 2019                                             |
| First version publication date | 03 February 2016                                         |
| Version creation reason        | • Changes to summary attachments<br>pubmed link attached |

### Trial information

#### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | OZR-2013-27 |
|-----------------------|-------------|

#### Additional study identifiers

|                                    |                                    |
|------------------------------------|------------------------------------|
| ISRCTN number                      | -                                  |
| ClinicalTrials.gov id (NCT number) | -                                  |
| WHO universal trial number (UTN)   | -                                  |
| Other trial identifiers            | Nederlands Trial Register: NTR4825 |

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,<br>31 104023430, r.wubbels@oogziekenhuis.nl |
| Scientific contact           | Rotterdam Ophthalmic Institute, The Rotterdam Eye Hospital,<br>31 104023430, r.wubbels@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:

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**Results analysis stage**

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|                                                      |               |
|------------------------------------------------------|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 21 May 2015   |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 22 April 2015 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 22 April 2015 |
| Was the trial ended prematurely?                     | No            |

Notes:

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**General information about the trial**

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Main objective of the trial:

Quantifying dabigatran levels and thrombin inhibiting activity in the vitreous and subretinal fluid after oral administration of dabigatran etexilate in patients with a retinal detachment.

Protection of trial subjects:

Patients at increased risk of bleeding were excluded.

Background therapy:

Coagulation factor thrombin is thought to play an important role in the development of proliferative vitreoretinopathy. The direct thrombin inhibitor dabigatran is, therefore, an interesting potential drug candidate. The objective of this study is to investigate whether oral administration of dabigatran etexilate in patients with a rhegmatogenous retinal detachment leads to clinical significant dabigatran levels and thrombin inhibiting activity in the vitreous and subretinal fluid.

Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 06 October 2014 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 28 |
| Worldwide total number of subjects   | 28              |
| EEA total number of subjects         | 28              |

Notes:

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**Subjects enrolled per age group**

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|                                           |    |
|-------------------------------------------|----|
| 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)                      | 17 |
| From 65 to 84 years                       | 11 |

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

## Subject disposition

### Recruitment

Recruitment details:

Patients with a rhegmatogenous retinal detachment, scheduled for a vitrectomy or scleral buckle surgery, were invited to participate.

### Pre-assignment

Screening details:

Use of anticoagulants or medication increasing the risk of gastro-intestinal bleeding.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 28 |
| Number of subjects completed | 28 |

### Period 1

|                              |                                 |
|------------------------------|---------------------------------|
| Period 1 title               | Overall trial. (overall period) |
| Is this the baseline period? | Yes                             |
| Allocation method            | Not applicable                  |
| Blinding used                | Not blinded                     |

### Arms

|           |                               |
|-----------|-------------------------------|
| Arm title | Intraocular dabigatran level. |
|-----------|-------------------------------|

Arm description:

All patients received 220 mg dabigatran. Depending on the type of surgery either a subretinal fluid sample (n=12) or a vitreous sample (n=16) could be taken for analysis.

|                                        |                       |
|----------------------------------------|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | Dabigatran etexilate. |
| Investigational medicinal product code | EU/1/08/442           |
| Other name                             | Pradaxa®              |
| Pharmaceutical forms                   | Capsule               |
| Routes of administration               | Oral use              |

Dosage and administration details:

Single oral dose (220 mg) administered 2 to 8 hours prior to surgery.

| Number of subjects in period 1 | Intraocular dabigatran level. |
|--------------------------------|-------------------------------|
| Started                        | 28                            |
| Completed                      | 28                            |

## Baseline characteristics

### Reporting groups

|                                |                |
|--------------------------------|----------------|
| Reporting group title          | Overall trial. |
| Reporting group description: - |                |

| Reporting group values                             | Overall trial. | Total |  |
|----------------------------------------------------|----------------|-------|--|
| Number of subjects                                 | 28             | 28    |  |
| 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                                    | 60.8           |       |  |
| standard deviation                                 | ± 7.6          | -     |  |
| Gender categorical                                 |                |       |  |
| Units: Subjects                                    |                |       |  |
| Female                                             | 6              | 6     |  |
| Male                                               | 22             | 22    |  |

### Subject analysis sets

|                            |                                           |
|----------------------------|-------------------------------------------|
| Subject analysis set title | Dabigatran level in the subretinal fluid. |
| Subject analysis set type  | Full analysis                             |

Subject analysis set description:

Dabigatran concentration in the subretinal fluid after oral administration of 220 mg dabigatran etexilate.

|                            |                                   |
|----------------------------|-----------------------------------|
| Subject analysis set title | Dabigatran level in the vitreous. |
| Subject analysis set type  | Full analysis                     |

Subject analysis set description:

Dabigatran concentration in the vitreous after oral administration of 220 mg dabigatran etexilate.

| Reporting group values                             | Dabigatran level in the subretinal fluid. | Dabigatran level in the vitreous. |  |
|----------------------------------------------------|-------------------------------------------|-----------------------------------|--|
| Number of subjects                                 | 12                                        | 16                                |  |
| Age categorical                                    |                                           |                                   |  |
| Units: Subjects                                    |                                           |                                   |  |
| In utero                                           |                                           |                                   |  |
| Preterm newborn infants (gestational age < 37 wks) |                                           |                                   |  |
| Newborns (0-27 days)                               |                                           |                                   |  |

|                                                                                                                                                                 |               |               |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|---------------|--|
| Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |               |               |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation                                                                                         | 58.2<br>± 8.1 | 62.8<br>± 6.8 |  |
| Gender categorical<br>Units: Subjects                                                                                                                           |               |               |  |
| Female<br>Male                                                                                                                                                  | 4<br>8        | 2<br>14       |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                            |                                           |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Reporting group title                                                                                                                                                                                      | Intraocular dabigatran level.             |
| Reporting group description:<br>All patients received 220 mg dabigatran. Depending on the type of surgery either a subretinal fluid sample (n=12) or a vitreous sample (n=16) could be taken for analysis. |                                           |
| Subject analysis set title                                                                                                                                                                                 | Dabigatran level in the subretinal fluid. |
| Subject analysis set type                                                                                                                                                                                  | Full analysis                             |
| Subject analysis set description:<br>Dabigatran concentration in the subretinal fluid after oral administration of 220 mg dabigatran etexilate.                                                            |                                           |
| Subject analysis set title                                                                                                                                                                                 | Dabigatran level in the vitreous.         |
| Subject analysis set type                                                                                                                                                                                  | Full analysis                             |
| Subject analysis set description:<br>Dabigatran concentration in the vitreous after oral administration of 220 mg dabigatran etexilate.                                                                    |                                           |

### Primary: Intraocular dabigatran level.

|                                                                                                                       |                               |
|-----------------------------------------------------------------------------------------------------------------------|-------------------------------|
| End point title                                                                                                       | Intraocular dabigatran level. |
| End point description:                                                                                                |                               |
|                                                                                                                       |                               |
| End point type                                                                                                        | Primary                       |
| End point timeframe:<br>A single dose of dabigatran etexilate (220 mg) is administered 2 to 8 hours prior to surgery. |                               |

| End point values                     | Dabigatran level in the subretinal fluid. | Dabigatran level in the vitreous. |  |  |
|--------------------------------------|-------------------------------------------|-----------------------------------|--|--|
| Subject group type                   | Subject analysis set                      | Subject analysis set              |  |  |
| Number of subjects analysed          | 12                                        | 16                                |  |  |
| Units: Concentration.                |                                           |                                   |  |  |
| arithmetic mean (standard deviation) | 5.8 (± 6)                                 | 1.8 (± 1)                         |  |  |

### Statistical analyses

|                                         |                                                                               |
|-----------------------------------------|-------------------------------------------------------------------------------|
| Statistical analysis title              | Comparison of dabigatran levels.                                              |
| Comparison groups                       | Dabigatran level in the subretinal fluid. v Dabigatran level in the vitreous. |
| Number of subjects included in analysis | 28                                                                            |
| Analysis specification                  | Post-hoc                                                                      |
| Analysis type                           | superiority                                                                   |
| P-value                                 | < 0.05                                                                        |
| Method                                  | Wilcoxon (Mann-Whitney)                                                       |

## Adverse events

### Adverse events information<sup>[1]</sup>

Timeframe for reporting adverse events:

Postoperative period.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 10 |
|--------------------|----|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | All participants. |
|-----------------------|-------------------|

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events were reported.

| Serious adverse events                            | All participants.                                                                                                                |  |  |
|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|--|--|
| Total subjects affected by serious adverse events |                                                                                                                                  |  |  |
| subjects affected / exposed                       | 3 / 28 (10.71%)                                                                                                                  |  |  |
| number of deaths (all causes)                     | 0                                                                                                                                |  |  |
| number of deaths resulting from adverse events    | 0                                                                                                                                |  |  |
| Eye disorders                                     |                                                                                                                                  |  |  |
| Retinal detachment (rhegmatogenous).              | Additional description: The reported SAE (i.e. a recurrent retinal detachment) is a known complication of the initial condition. |  |  |
| subjects affected / exposed                       | 3 / 28 (10.71%)                                                                                                                  |  |  |
| occurrences causally related to treatment / all   | 3 / 3                                                                                                                            |  |  |
| deaths causally related to treatment / all        | 0 / 0                                                                                                                            |  |  |

Frequency threshold for reporting non-serious adverse events: 0.05 %

| Non-serious adverse events                            | All participants. |  |  |
|-------------------------------------------------------|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 0 / 28 (0.00%)    |  |  |

## 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

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

|                                                                                      |
|--------------------------------------------------------------------------------------|
| This was a pilot study to demonstrate that dabigatran reaches the intraocular space. |
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Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28128536>