



## Clinical trial results:

### Intravitreal Aflibercept (Eylea®) for therapy of choroidal neovascularization and fibrovascular proliferation in patients with Pseudoxanthoma elasticum

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-005263-33 |
| Trial protocol           | DE             |
| Global end of trial date | 02 July 2018   |

#### Results information

|                                   |  |
|-----------------------------------|--|
| Result version number             | v1 (current)   |
| This version publication date     | 09 February 2022   |
| First version publication date    | 09 February 2022   |
| Summary attachment (see zip file) | Publication (Aflibercept for choroidal neovascularizations secondary to pseudoxanthoma elasticum- a prospective study.pdf) |

#### Trial information

##### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | AUG-201202-EyNeP |
|-----------------------|------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02537054 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Universitätsklinikum Bonn   |
| Sponsor organisation address | Venusberg-Campus 1, Bonn, Germany,  |
| Public contact               | Dr. med. Christoph Coch, Studienzentrale SZB, 0049 22828716040, ccoch@uni-bonn.de |
| Scientific contact           | Dr. med. Christoph Coch, Studienzentrale SZB, 0049 22828716040, ccoch@uni-bonn.de |

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                       | 19 November 2019 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 02 July 2018     |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 02 July 2018     |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The purpose of this study is to determine whether Aflibercept (Eylea) is effective in the treatment of choroidal neovascularization and fibrovascular proliferation in patients with pseudoxanthoma elasticum (PXE) in terms of preservation or improvement of visual acuity.

Protection of trial subjects:

The study medication was authorized for the treatment of various retinal diseases before. Each patient was informed about the study in detail, the patient and the investigation signed the informed consent form. A patient's insurance was in place. Adverse events were documented regularly.

Background therapy: -

Evidence for comparator:

The development of intravitreal anti-vascular endothelial growth factor (VEGF) agents has significantly improved the visual prognosis of patients with PXE-related CNV. Good evidence exists for the efficacy of intravitreal bevacizumab and ranibizumab. Another intravitreal VEGF inhibitor is aflibercept, which is a fusion protein of the extracellular domains of the VEGF receptor 1 and 2 and the Fc fragment of human IgG potentially blocking all isoforms of VEGF A and placental growth factor. The efficacy of intravitreal aflibercept is proven for CNV secondary to AMD and myopia. Evidence for efficacy for the treatment of CNV secondary to angioid streaks in PXE patients is limited to a few case reports. In addition, there is one small prospective study on ranibizumab-pretreated patients with a CNV secondary to angioid streaks reporting favorable outcomes, which, however, was not specific for PXE patients. Therefore, it was the aim of this study to prospectively investigate the use of intravitreal aflibercept for treatment-naïve and pretreated CNV in patients with PXE.

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 01 May 2015 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | No          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 15 |
| Worldwide total number of subjects   | 15          |
| EEA total number of subjects         | 15          |

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)                     | 14 |
| From 65 to 84 years                      | 1  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited between September 2015 and July 2017 at the Department of Ophthalmology, University of Bonn, which is a tertiary referral center for patients with PXE in Germany.

### Pre-assignment

Screening details:

The inclusion criteria were the diagnosis of an active CNV secondary to PXE and age between 18 and 65 years. The diagnosis of PXE was based on typical ophthalmologic findings and confirmed by genetic testing.

### Period 1

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

Blinding implementation details:

Prospective, open-label, uncontrolled, non-randomized interventional clinical trial.

### Arms

|           |            |
|-----------|------------|
| Arm title | Single Arm |
|-----------|------------|

Arm description:

This was a prospective, open-label, uncontrolled, non-randomized interventional clinical trial.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Aflibercept (2 mg) |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Injection          |
| Routes of administration               | Intravitreal use   |

Dosage and administration details:

Intravitreal injection of 2 mg aflibercept

|                                       |            |
|---------------------------------------|------------|
| <b>Number of subjects in period 1</b> | Single Arm |
| Started                               | 15         |
| Completed                             | 15         |

## Baseline characteristics

### Reporting groups

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

| Reporting group values                             | Overall trial | Total |  |
|--|---------------|-------|--|
| Number of subjects                                 | 15            | 15    |  |
| Age categorical                                    |               |       |  |
| Units: Subjects                                    |               |       |  |
| In utero   | 0             | 0     |  |
| Preterm newborn infants (gestational age < 37 wks) | 0             | 0     |  |
| Newborns (0-27 days)                               | 0             | 0     |  |
| Infants and toddlers (28 days-23 months)           | 0             | 0     |  |
| Children (2-11 years)                              | 0             | 0     |  |
| Adolescents (12-17 years)                          | 0             | 0     |  |
| Adults (18-64 years)                               | 14            | 14    |  |
| From 65-84 years                                   | 1             | 1     |  |
| 85 years and over                                  | 0             | 0     |  |
| Age continuous                                     |               |       |  |
| Units: years                                       |               |       |  |
| arithmetic mean                                    | 53            |       |  |
| full range (min-max)                               | 22 to 65      | -     |  |
| Gender categorical                                 |               |       |  |
| Units: Subjects                                    |               |       |  |
| Female   | 10            | 10    |  |
| Male   | 5             | 5     |  |

### Subject analysis sets

|                            |               |
|----------------------------|---------------|
| Subject analysis set title | Full analysis |
| Subject analysis set type  | Full analysis |

Subject analysis set description:

The primary endpoint was change of BCVA after 12 months compared to baseline. Secondary outcomes were change compared to baseline of central retinal thickness, leakage from CNV, retinal sensitivity, and vision-related quality of life.

| Reporting group values                             | Full analysis |  |  |
|--|---------------|--|--|
| Number of subjects                                 | 15            |  |  |
| 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)      | 14       |  |  |
| From 65-84 years          | 1        |  |  |
| 85 years and over         |          |  |  |
| Age continuous            |          |  |  |
| Units: years              |          |  |  |
| arithmetic mean           | 53       |  |  |
| full range (min-max)      | 22 to 65 |  |  |
| Gender categorical        |          |  |  |
| Units: Subjects           |          |  |  |
| Female                    | 10       |  |  |
| Male                      | 5        |  |  |

## End points

### End points reporting groups

|   |               |
|---|---------------|
| Reporting group title   | Single Arm    |
| Reporting group description:<br>This was a prospective, open-label, uncontrolled, non-randomized interventional clinical trial.   |               |
| Subject analysis set title  | Full analysis |
| Subject analysis set type   | Full analysis |
| Subject analysis set description:<br>The primary endpoint was change of BCVA after 12 months compared to baseline. Secondary outcomes were change compared to baseline of central retinal thickness, leakage from CNV, retinal sensitivity, and vision-related quality of life. |               |

### Primary: Change of BCVA compared to baseline

|                                   |                                     |
|-----------------------------------|-------------------------------------|
| End point title                   | Change of BCVA compared to baseline |
| End point description:            |                                     |
| End point type                    | Primary                             |
| End point timeframe:<br>12 months |                                     |

| End point values            | Single Arm      | Full analysis        |  |  |
|-----------------------------|-----------------|----------------------|--|--|
| Subject group type          | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed | 15              | 15                   |  |  |
| Units: Whole                | 15              | 15                   |  |  |

|                            |           |
|----------------------------|-----------|
| Attachments (see zip file) | EyNep.pdf |
|----------------------------|-----------|

### Statistical analyses

|  |                            |
|--|----------------------------|
| Statistical analysis title   | Statistical analysis       |
| Statistical analysis description:<br>Continuous outcome measures (BCVA, central retinal thickness, retinal sensitivity, and quality of life) at baseline and month 12 are described using means and standard deviations (SD). Mean differences between baseline and month 12 were calculated along with 95% confidence intervals. The measures at the two points in time were compared using Wilcoxon rank-sum tests. A two-sided $p < 0.05$ was considered significant. |                            |
| Comparison groups  | Single Arm v Full analysis |
| Number of subjects included in analysis  | 30                         |
| Analysis specification   | Pre-specified              |
| Analysis type  | other                      |
| P-value  | $< 0.05$                   |
| Method   | Wilcoxon (Mann-Whitney)    |

**Secondary: Change of central retinal thickness, leakage from CNV, retinal sensitivity, vision-related quality of life**

|                 |  |
|-----------------|--|
| End point title | Change of central retinal thickness, leakage from CNV, retinal sensitivity, vision-related quality of life |
|-----------------|--|

End point description:

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

12 months

|                             |                 |                      |  |  |
|-----------------------------|-----------------|----------------------|--|--|
| <b>End point values</b>     | Single Arm      | Full analysis        |  |  |
| Subject group type          | Reporting group | Subject analysis set |  |  |
| Number of subjects analysed | 15              | 15                   |  |  |
| Units: Whole                | 15              | 15                   |  |  |

|                                   |           |
|-----------------------------------|-----------|
| <b>Attachments (see zip file)</b> | EyNep.pdf |
|-----------------------------------|-----------|

**Statistical analyses**

|                                   |                      |
|-----------------------------------|----------------------|
| <b>Statistical analysis title</b> | Statistical analysis |
|-----------------------------------|----------------------|

Statistical analysis description:

Continuous outcome measures (BCVA, central retinal thickness, retinal sensitivity, and quality of life) at baseline and month 12 are described using means and standard deviations (SD). Mean differences between baseline and month 12 were calculated along with 95% confidence intervals. The measures at the two points in time were compared using Wilcoxon rank-sum tests. A two-sided  $p < 0.05$  was considered significant.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Single Arm v Full analysis |
| Number of subjects included in analysis | 30                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other                      |
| P-value                                 | $< 0.05$                   |
| Method                                  | Wilcoxon (Mann-Whitney)    |

|                                   |                      |
|-----------------------------------|----------------------|
| <b>Statistical analysis title</b> | Statistical analysis |
|-----------------------------------|----------------------|

Statistical analysis description:

Continuous outcome measures (BCVA, central retinal thickness, retinal sensitivity, and quality of life) at baseline and month 12 are described using means and standard deviations (SD). Mean differences between baseline and month 12 were calculated along with 95% confidence intervals. The measures at the two points in time were compared using Wilcoxon rank-sum tests. A two-sided  $p < 0.05$  was considered significant.

|                   |                            |
|-------------------|----------------------------|
| Comparison groups | Single Arm v Full analysis |
|-------------------|----------------------------|



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 30                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | < 0.05                  |
| Method                                  | Wilcoxon (Mann-Whitney) |

|                                   |                      |
|-----------------------------------|----------------------|
| <b>Statistical analysis title</b> | Statistical analysis |
|-----------------------------------|----------------------|

Statistical analysis description:

Continuous outcome measures (BCVA, central retinal thickness, retinal sensitivity, and quality of life) at baseline and month 12 are described using means and standard deviations (SD). Mean differences between baseline and month 12 were calculated along with 95% confidence intervals. The measures at the two points in time were compared using Wilcoxon rank-sum tests. A two-sided  $p < 0.05$  was considered significant.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Single Arm v Full analysis |
| Number of subjects included in analysis | 30                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other                      |
| P-value                                 | < 0.05                     |
| Method                                  | Wilcoxon (Mann-Whitney)    |

|                                   |                      |
|-----------------------------------|----------------------|
| <b>Statistical analysis title</b> | Statistical analysis |
|-----------------------------------|----------------------|

Statistical analysis description:

Differences regarding leakage from a CNV on FA were compared using a McNemar test.

|   |                            |
|---|----------------------------|
| Comparison groups                       | Single Arm v Full analysis |
| Number of subjects included in analysis | 30                         |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other                      |
| P-value                                 | < 0.05                     |
| Method                                  | McNemar                    |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

September 2015 - July 2017

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

### Reporting groups

|                       |               |
|-----------------------|---------------|
| Reporting group title | Entire Cohort |
|-----------------------|---------------|

Reporting group description: -

| Serious adverse events   | Entire Cohort   |  |  |
|--|---|--|--|
| Total subjects affected by serious adverse events              |   |  |  |
| subjects affected / exposed                                    | 2 / 15 (13.33%)   |  |  |
| number of deaths (all causes)                                  | 0   |  |  |
| number of deaths resulting from adverse events                 |   |  |  |
| Surgical and medical procedures                                |   |  |  |
| Intracardiac catheter after an ST-elevation on ERG examination | Additional description: The causality with the study medication/procedure was graded as unlikely. |  |  |
| subjects affected / exposed                                    | 1 / 15 (6.67%)  |  |  |
| occurrences causally related to treatment / all                | 0 / 1   |  |  |
| deaths causally related to treatment / all                     | 0 / 0   |  |  |
| Surgery for an umbilical hernia                                |   |  |  |
| subjects affected / exposed                                    | 1 / 15 (6.67%)  |  |  |
| occurrences causally related to treatment / all                | 0 / 1   |  |  |
| deaths causally related to treatment / all                     | 0 / 0   |  |  |

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

| Non-serious adverse events                            | Entire Cohort  |  |  |
|---|--|--|--|
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 5 / 15 (33.33%)  |  |  |
| Eye disorders   |  |  |  |
| Ocular adverse events                                 | Additional description: 5 ocular adverse events were documented that were likely associated with the study medication/procedure (increased intraocular pressure in 2 participants, mild conjunctival hemorrhage in 2 participants and foreign body sensation after injection in 1. |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 5 / 15 (33.33%) |  |  |
| occurrences (all)           | 5               |  |  |

## 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/31863395>