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

Number of subjects in period 1	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:

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:

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:

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:

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

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:

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.

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Statistical analysis description:

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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)

Statistical analysis title	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)

Statistical analysis title	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 occurrences (all)	5 / 15 (33.33%) 5		

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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31863395