



Clinical trial results:

A Phase IV, prospective, open-label, uncontrolled, European Study in patients with neovascular Age-related macular degeneration (nAMD), evaluating the efficacy and safety of switching from intravitreal Aflibercept to Ranibizumab 0.5 mg.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2014-001085-10 |
| Trial protocol | DE |
| Global end of trial date | 14 September 2017 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 30 September 2018 |
| First version publication date | 30 September 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CRFB002AGB17 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02161575 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |

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 | 14 September 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 September 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate whether treatment with IVT ranibizumab 0.5 mg was associated with improvement (i.e. reduction at Day 90 from baseline) in central subfield retinal thickness (CSRT), as determined by OCT after 3 monthly injections of ranibizumab.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 28 August 2014 |
| 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 | United Kingdom: 87 |
| Country: Number of subjects enrolled | Germany: 16 |
| Worldwide total number of subjects | 103 |
| EEA total number of subjects | 103 |

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) | 6 |
| From 65 to 84 years | 84 |

| | |
|-------------------|----|
| 85 years and over | 13 |
|-------------------|----|

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 22 sites located in the United Kingdom and 6 sites located in Germany. A total of 103 patients received at least 1 dose of study drug.

Pre-assignment

Screening details:

Of the 103 patients who received at least 1 dose of study drug, 3 patients did not have any post-baseline safety or CSRT assessments and were therefore excluded from the SAF and FAS, in accordance with the analysis set definitions. Therefore, 100 patients were included in the SAF and FAS.

Period 1

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

Arms

| | |
|-----------|-------------|
| Arm title | Ranibizumab |
|-----------|-------------|

Arm description:

All patients received 3 monthly intraveal injections of 0.5mg ranibizumab followed by monthly injections of ranibizumab 0.5mg for a further 3 months on a prn (as required) basis, as determined by the study doctor.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Ranibizumab |
| Investigational medicinal product code | RFB002 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intraocular use |

Dosage and administration details:

Intraveal injections of 0.5mg ranibizumab

| Number of subjects in period 1 ^[1] | Ranibizumab |
|---|-------------|
| Started | 100 |
| Full Analysis Set (FAS) Population | 100 |
| Safety (SAF) Population | 100 |
| Completed | 92 |
| Not completed | 8 |
| Adverse event, non-fatal | 2 |
| Protocol deviation | 5 |
| Lack of efficacy | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of the 103 patients who received at least 1 dose of study drug, 3 patients did not have any post-baseline safety or CSRT assessments and were therefore excluded from the SAF and FAS.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Ranibizumab |
|-----------------------|-------------|

Reporting group description:

All patients received 3 monthly intraveal injections of 0.5mg ranibizumab followed by monthly injections of ranibizumab 0.5mg for a further 3 months on a prn (as required) basis, as determined by the study doctor.

| Reporting group values | Ranibizumab | Total | |
|---|-------------|-------|--|
| Number of subjects | 100 | 100 | |
| 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) | 6 | 6 | |
| From 65-84 years | 81 | 81 | |
| 85 years and over | 13 | 13 | |
| Age Continuous Units: years | | | |
| arithmetic mean | 77 | | |
| standard deviation | ± 6.51 | - | |
| Sex: Female, Male Units: Subjects | | | |
| Female | 55 | 55 | |
| Male | 45 | 45 | |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Caucasian | 99 | 99 | |
| Asian | 1 | 1 | |

End points

End points reporting groups

| | |
|---|-------------|
| Reporting group title | Ranibizumab |
| Reporting group description: All patients received 3 monthly intraveal injections of 0.5mg ranibizumab followed by monthly injections of ranibizumab 0.5mg for a further 3 months on a prn (as required) basis, as determined by the study doctor. | |

Primary: Change in Central Subfield Retinal Thickness (CSRT) from Baseline to Day 90.

| | |
|--|---|
| End point title | Change in Central Subfield Retinal Thickness (CSRT) from Baseline to Day 90. ^[1] |
| End point description: Measurement of the change in CSRT, determined by high definition optical coherence tomography (HD-OCT) after 3 monthly injections of ranibizumab. OCT is a non-invasive technique which can determine and measure thickness of the retina. A negative change from Baseline indicates an improvement (less retinal fluid and lower disease activity). Data collected on the study eye were used for the evaluation of efficacy. | |
| End point type | Primary |
| End point timeframe: Baseline and Day 90 | |
| 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: No statistical analyses provided as it was a single arm trial. | |

| End point values | Ranibizumab | | | |
|--------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 97 | | | |
| Units: micrometer | | | | |
| median (full range (min-max)) | | | | |
| Baseline | 384.00 (154.0 to 975.0) | | | |
| Day 90 | 318.00 (170.0 to 832.0) | | | |
| Change from Baseline to Day 90 | -30.75 (-386.0 to 78.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Subfoveal Retinal Thickness (SRT) from Baseline to Day 180

| | |
|---|--|
| End point title | Change in Subfoveal Retinal Thickness (SRT) from Baseline to Day 180 |
| End point description: Measurement of change in SRT from Baseline to Day 180 as determined by high definition optical coherence tomography (HD-OCT). A reduction indicates an improvement in overall disease activity. Data collected on the study eye were used for the evaluation of efficacy. | |

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 180 | |

| | | | | |
|-------------------------------------|--------------------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: micrometer | | | | |
| median (full range (min-max)) | | | | |
| SRT at Baseline | 346.00 (69.0 to 944.5) | | | |
| SRT at Day 180 | 302.00 (41.5 to 876.5) | | | |
| SRT change from Baseline to Day 180 | -23.50 (-464.0 to 306.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Central Subfield Retinal Thickness (CSRT) from Baseline to Day 180

| | |
|--|--|
| End point title | Change in Central Subfield Retinal Thickness (CSRT) from Baseline to Day 180 |
| End point description: | |
| Measurement of change in CSRT from Baseline to Day 180 as determined by high definition optical coherence tomography (HD-OCT). A reduction indicates an improvement in overall disease activity. Data collected on the study eye were used for the evaluation of efficacy. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 180 | |

| | | | | |
|--------------------------------------|--------------------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: micrometer | | | | |
| median (full range (min-max)) | | | | |
| CSRT at Baseline | 384.00 (154.0 to 975.0) | | | |
| CSRT at Day 180 | 343.00 (194.0 to 842.0) | | | |
| CSRT change from Baseline to Day 180 | -28.00 (-271.0 to 171.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Central Subfield Retinal Volume (CSRV) from Baseline to Day 180

| | |
|--|---|
| End point title | Change in Central Subfield Retinal Volume (CSRV) from Baseline to Day 180 |
| End point description: Measurement of change in CSRV from Baseline to Day 180 as determined by high definition optical coherence tomography (HD-OCT). A reduction indicates an improvement in overall disease activity. Data collected on the study eye were used for the evaluation of efficacy. | |
| End point type | Secondary |
| End point timeframe: Baseline and Day 180 | |

| | | | | |
|--------------------------------------|---------------------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: cubic micrometer | | | | |
| median (full range (min-max)) | | | | |
| CSRV at Baseline | 0.3050 (0.120 to 11.600) | | | |
| CSRV at Day 180 | 0.2750 (0.115 to 11.400) | | | |
| CSRV change from Baseline to Day 180 | -0.0200 (-1.600 to 0.135) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Intraretinal Fluid assessed at Baseline and Day 180

| | |
|--|---|
| End point title | Number of patients with Intraretinal Fluid assessed at Baseline and Day 180 |
| End point description: Presence or absence of qualitative OCT parameter Intraretinal Fluid. Data collected on the study eye were used for the evaluation of efficacy. | |
| End point type | Secondary |
| End point timeframe: Baseline and Day 180 | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: Participants | | | | |
| Baseline Yes, Definitive | 32 | | | |
| Day 180 Yes, Definitive | 24 | | | |
| Baseline Yes, Subtle | 11 | | | |
| Day 180 Yes, Subtle | 15 | | | |
| Baseline No | 56 | | | |
| Day 180 No | 55 | | | |
| Baseline Questionable | 1 | | | |
| Day 180 Questionable | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Subretinal Fluid assessed at Baseline and Day 180

| | |
|--|---|
| End point title | Number of patients with Subretinal Fluid assessed at Baseline and Day 180 |
| End point description: Presence or absence of qualitative OCT parameter Subretinal Fluid. Data collected on the study eye were used for the evaluation of efficacy. | |
| End point type | Secondary |
| End point timeframe: Baseline to Day 180 | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: Participants | | | | |
| Baseline Yes, Definitive | 83 | | | |
| Day 180 Yes, Definitive | 49 | | | |
| Baseline Yes, Subtle | 5 | | | |
| Day 180 Yes, Subtle | 15 | | | |
| Baseline No | 12 | | | |
| Day 180 No | 30 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Intraretinal/Subretinal Fluid Within the Central Subfield Fluid assessed at baseline and Day 180

| | |
|-----------------|--|
| End point title | Number of patients with Intraretinal/Subretinal Fluid Within the Central Subfield Fluid assessed at baseline and Day 180 |
|-----------------|--|

End point description:

Presence or absence of qualitative OCT parameter Intraretinal/Subretinal Fluid Within the Central Subfield. Data collected on the study eye were used for the evaluation of efficacy.

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

End point timeframe:

Baseline and Day 180

| End point values | Ranibizumab | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: Participants | | | | |
| Baseline Yes, Definitive | 38 | | | |
| Day 180 Yes, Definitive | 26 | | | |
| Baseline Yes, Subtle | 6 | | | |
| Day 180 Yes, Subtle | 12 | | | |
| Baseline No | 5 | | | |
| Day 180 No | 15 | | | |
| Baseline Questionable | 1 | | | |
| Day 180 Questionable | 1 | | | |
| Baseline NA | 50 | | | |
| Day 180 NA | 40 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Pigment Epithelial Detachments assessed at baseline and Day 180

| | |
|-----------------|---|
| End point title | Number of patients with Pigment Epithelial Detachments assessed at baseline and Day 180 |
|-----------------|---|

End point description:

Presence or absence of qualitative OCT parameter Pigment Epithelial Detachments. Data collected on the study eye were used for the evaluation of efficacy.

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

End point timeframe:

Baseline and Day 180

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: Participants | | | | |
| Baseline Yes, Definitive | 86 | | | |
| Day 180 Yes, Definitive | 80 | | | |
| Baseline Yes, Subtle | 2 | | | |
| Day 180 Yes, Subtle | 4 | | | |
| Baseline No | 12 | | | |
| Day 180 No | 8 | | | |
| Baseline Not gradable | 0 | | | |
| Day 180 Not gradable | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patients with Dry Retina assessed at baseline and Day 180

| | |
|--|---|
| End point title | Number of patients with Dry Retina assessed at baseline and Day 180 |
| End point description: Presence or absence of qualitative OCT parameter Dry Retina. Data collected on the study eye were used for the evaluation of efficacy. | |
| End point type | Secondary |
| End point timeframe: Baseline and Day 180 | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: Participants | | | | |
| Baseline Yes, Definitive | 0 | | | |
| Day 180 Yes, Definitive | 0 | | | |
| Baseline No | 100 | | | |
| Day 180 No | 94 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Maximum PED Height from Baseline to Day 180

| | |
|---|---|
| End point title | Change in Maximum PED Height from Baseline to Day 180 |
| End point description: Change from Baseline to Day 180 in Maximum Pigment Epithelial Detachment (PED) Height. Data | |

collected on the study eye were used for the evaluation of efficacy.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 180 | |

| | | | | |
|---------------------------------|-------------------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: micrometer | | | | |
| median (full range (min-max)) | | | | |
| Baseline | 236.00 (66.5 to 674.0) | | | |
| Day 180 | 203.50 (63.5 to 705.0) | | | |
| Change from Baseline to Day 180 | -2.50 (-336.5 to 131.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Maximum PED Diameter from Baseline to Day 180

| | |
|--|---|
| End point title | Change in Maximum PED Diameter from Baseline to Day 180 |
| End point description: | |
| Change from Baseline to Day 180 in Maximum Pigment Epithelial Detachment (PED) Diameter. Data collected on the study eye were used for the evaluation of efficacy. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 180 | |

| | | | | |
|---------------------------------|---------------------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: micrometer | | | | |
| median (full range (min-max)) | | | | |
| Baseline | 2205.00 (0.0 to 4877.0) | | | |
| Day 180 | 2428.00 (471.0 to 4683.0) | | | |
| Change from Baseline to Day 180 | 59.50 (-1007.0 to 2756.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Maximum IRC Height from Baseline to Day 180

| | |
|-----------------|---|
| End point title | Change in Maximum IRC Height from Baseline to Day 180 |
|-----------------|---|

End point description:

Change from Baseline to Day 180 in Maximum Intraretinal Cyst (IRC) Height. Data collected on the study eye were used for the evaluation of efficacy.

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

End point timeframe:

Baseline and Day 180

| End point values | Ranibizumab | | | |
|---------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: micrometer | | | | |
| median (full range (min-max)) | | | | |
| Baseline | 121.50 (21.0 to 280.5) | | | |
| Day 180 | 105.50 (25.5 to 485.0) | | | |
| Change from Baseline to Day 180 | 0.00 (-223.5 to 235.0) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Best Corrected Visual Acuity (BCVA) in the Study Eye

| | |
|-----------------|--|
| End point title | Change in Best Corrected Visual Acuity (BCVA) in the Study Eye |
|-----------------|--|

End point description:

Change in overall BCVA score from Baseline to Day 180, and from Day 90 to Day 180 in the Study Eye.

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

End point timeframe:

Baseline, Day 90 and Day 180

| End point values | Ranibizumab | | | |
|-------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: letters | | | | |
| median (full range (min-max)) | | | | |
| Baseline | 71.5 (36 to 90) | | | |
| Day 90 | 74.0 (32 to 87) | | | |

| | | | | |
|---------------------------------|-----------------|--|--|--|
| Day 180 | 75.0 (32 to 90) | | | |
| Change from Baseline to Day 180 | 1.0 (-31 to 35) | | | |
| Change from Day 90 to Day 180 | 0.0 (-25 to 24) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change in ETDRS Letters for Study Eye from Baseline to Day 180

| | |
|---|--|
| End point title | Change in ETDRS Letters for Study Eye from Baseline to Day 180 |
| End point description: | |
| Number of patients gaining at least 15 letters from Baseline to Day 180 | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and Day 180 | |

| End point values | Ranibizumab | | | |
|-------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: Participants | | | | |
| >=15 (Gain of at least 15 letters) | 11 | | | |
| 10 to <15 | 6 | | | |
| 5 to <10 | 17 | | | |
| 0 to <5 | 25 | | | |
| >-15 to <0 | 31 | | | |
| <=-15 (Loss of at least 15 letters) | 7 | | | |
| NA | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of ocular TEAEs in the Study Eye reported by ≥2% patients from Baseline to Day 180

| | |
|--|--|
| End point title | Incidence of ocular TEAEs in the Study Eye reported by ≥2% patients from Baseline to Day 180 |
| End point description: | |
| Incidence of ocular Treatment Emergent Adverse Events (TEAEs) in the study eye reported by ≥2% patients by preferred term. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Day 180 | |

| | | | | |
|---------------------------------|-----------------|--|--|--|
| End point values | Ranibizumab | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 100 | | | |
| Units: Participants | | | | |
| Eye pain | 3 | | | |
| Visual impairment | 3 | | | |
| Blepharitis | 2 | | | |
| Posterior capsule opacification | 2 | | | |
| Intraocular pressure increased | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.1 |

Reporting groups

| | |
|-----------------------|---------------------|
| Reporting group title | Overall Ranibizumab |
|-----------------------|---------------------|

Reporting group description:

Overall Ranibizumab

| Serious adverse events | Overall Ranibizumab | | |
|---|---------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 100 (10.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Investigations | | | |
| CATHETERISATION CARDIAC | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| PROSTATIC SPECIFIC ANTIGEN INCREASED | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| CONTUSION | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| FALL | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 100 (3.00%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| POST PROCEDURAL HAEMATOMA | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| ACUTE MYOCARDIAL INFARCTION | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| ATRIAL FLUTTER | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| UMBILICAL HERNIA REPAIR | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| VAGINAL PROLAPSE REPAIR | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| TRANSIENT ISCHAEMIC ATTACK | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---------------------------------------|--|--|
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 100 (1.00%) 0 / 1 0 / 0 | | |
| General disorders and administration site conditions NON-CARDIAC CHEST PAIN subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 100 (1.00%) 0 / 1 0 / 0 | | |
| Eye disorders RETINAL HAEMORRHAGE subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 100 (1.00%) 0 / 1 0 / 0 | | |
| Gastrointestinal disorders DIARRHOEA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 100 (1.00%) 0 / 1 0 / 0 | | |
| UPPER GASTROINTESTINAL HAEMORRHAGE subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 100 (1.00%) 0 / 1 0 / 0 | | |
| VOMITING subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 100 (1.00%) 0 / 1 0 / 0 | | |
| Reproductive system and breast disorders PROSTATOMEGALY subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 100 (1.00%) 0 / 1 0 / 0 | | |
| Renal and urinary disorders | | | |

| | | | |
|---|-----------------|--|--|
| URINARY RETENTION | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| PNEUMONIA | | | |
| subjects affected / exposed | 1 / 100 (1.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1.9 %

| | | | |
|---|---------------------|--|--|
| Non-serious adverse events | Overall Ranibizumab | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 52 / 100 (52.00%) | | |
| Investigations | | | |
| BLOOD PRESSURE SYSTOLIC INCREASED | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | | |
| occurrences (all) | 2 | | |
| BLOOD PRESSURE INCREASED | | | |
| subjects affected / exposed | 4 / 100 (4.00%) | | |
| occurrences (all) | 5 | | |
| HEART RATE DECREASED | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | | |
| occurrences (all) | 2 | | |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | | |
| occurrences (all) | 2 | | |
| INTRAOCULAR PRESSURE INCREASED | | | |
| subjects affected / exposed | 3 / 100 (3.00%) | | |
| occurrences (all) | 4 | | |
| Vascular disorders | | | |
| HYPERTENSION | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | | |
| occurrences (all) | 3 | | |

| | | | |
|---|--|--|--|
| Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) HEADACHE subjects affected / exposed occurrences (all) | 2 / 100 (2.00%) 2 3 / 100 (3.00%) 3 | | |
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) | 2 / 100 (2.00%) 2 | | |
| General disorders and administration site conditions FATIGUE subjects affected / exposed occurrences (all) | 2 / 100 (2.00%) 2 | | |
| Eye disorders BLEPHARITIS subjects affected / exposed occurrences (all) DRY EYE subjects affected / exposed occurrences (all) EYE PAIN subjects affected / exposed occurrences (all) POSTERIOR CAPSULE OPACIFICATION subjects affected / exposed occurrences (all) VISUAL IMPAIRMENT subjects affected / exposed occurrences (all) | 6 / 100 (6.00%) 6 3 / 100 (3.00%) 3 3 / 100 (3.00%) 3 2 / 100 (2.00%) 2 3 / 100 (3.00%) 3 | | |
| Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all) | 7 / 100 (7.00%) 7 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| BACK PAIN | | | |
| subjects affected / exposed | 3 / 100 (3.00%) | | |
| occurrences (all) | 3 | | |
| INTERVERTEBRAL DISC PROTRUSION | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | | |
| occurrences (all) | 2 | | |
| Infections and infestations | | | |
| CYSTITIS | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | | |
| occurrences (all) | 2 | | |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 7 / 100 (7.00%) | | |
| occurrences (all) | 7 | | |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 9 / 100 (9.00%) | | |
| occurrences (all) | 9 | | |
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 2 / 100 (2.00%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 30 March 2015 | The permitted time period for a historical OCT volume scan was changed from ≤ 14 days to ≤ 28 days before the date of first injection of aflibercept to the study eye. The definition of pathologic myopia in Exclusion Criterion 15 was changed from ≥ 8 dioptres to ≥ 6 dioptres. |
| 11 May 2016 | The sample size calculation was amended, and the study population was changed from 162 to 124 patients. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported