



## Clinical trial results:

**A randomized, double-masked, sham-controlled phase 3b/4 study of the efficacy, safety, and tolerability of intravitreal aflibercept monotherapy compared to aflibercept with adjunctive photodynamic therapy as indicated in subjects with polypoidal choroidal vasculopathy (PLANET)**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-004464-54 |
| Trial protocol           | HU DE          |
| Global end of trial date | 07 July 2017   |

### Results information

|                                |                                                                                                                                                                                                                                   |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Result version number          | v2 (current)                                                                                                                                                                                                                      |
| This version publication date  | 01 February 2019                                                                                                                                                                                                                  |
| First version publication date | 18 July 2018                                                                                                                                                                                                                      |
| Version creation reason        | <ul style="list-style-type: none"><li>New data added to full data set</li></ul> The description of endpoint 'Change of Central subfield thickness (CST) on Optical coherence tomography (OCT) from baseline to Week 52' is added. |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY86-5321/16995 |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |                             |
|------------------------------------|-----------------------------|
| ISRCTN number                      | -                           |
| ClinicalTrials.gov id (NCT number) | NCT02120950                 |
| WHO universal trial number (UTN)   | -                           |
| Other trial identifiers            | Informal study name: PLANET |

Notes:

#### Sponsors

|                              |                                                                                                                 |
|------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Bayer AG                                                                                                        |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,                                                              |
| Public contact               | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com, Bayer AG, clinical-trials-contact@bayer.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                       | 07 July 2017   |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 12 August 2016 |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 07 July 2017   |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

Primary objective of the study was to collect data reflecting the efficacy and safety of aflibercept with and without photodynamic therapy (PDT) rescue treatment in subjects diagnosed with the polypoidal choroidal vasculopathy (PCV) subtype of wet age-related macular degeneration (AMD) and to explore whether intravitreally administered aflibercept monotherapy is non-inferior to that of aflibercept plus PDT (as indicated) based upon best-corrected visual acuity (BCVA) in subjects diagnosed with the PCV subtype of AMD.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

|                                                           |             |
|-----------------------------------------------------------|-------------|
| Actual start date of recruitment                          | 29 May 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 | Japan: 159             |
| Country: Number of subjects enrolled | Australia: 24          |
| Country: Number of subjects enrolled | Korea, Republic of: 72 |
| Country: Number of subjects enrolled | Taiwan: 37             |
| Country: Number of subjects enrolled | Hong Kong: 14          |
| Country: Number of subjects enrolled | Singapore: 13          |
| Country: Number of subjects enrolled | Germany: 1             |
| Country: Number of subjects enrolled | Hungary: 13            |
| Worldwide total number of subjects   | 333                    |
| EEA total number of subjects         | 14                     |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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)                      | 77  |
| From 65 to 84 years                       | 245 |
| 85 years and over                         | 11  |

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at 62 study centers in Germany, Japan, Australia, Hungary, Republic of Korea, Taiwan, Hong Kong, and Singapore between 29 May 2014 (first subject first visit) and 12 August 2016 (last subject last visit).

### Pre-assignment

Screening details:

Overall, 428 subjects were screened, of them 95 were failed in screening, remaining 333 subjects were allocated to treatment, of them 15 subjects were treated as run-in treatment, until the subjects were randomized and received treatment, remaining 318 were randomized and treated.

### Period 1

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 1 title               | Overall Trial (overall period)                                |
| Is this the baseline period? | Yes                                                           |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind                                                  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

|                              |                                               |
|------------------------------|-----------------------------------------------|
| Are arms mutually exclusive? | Yes                                           |
| <b>Arm title</b>             | Aflibercept + Sham Photodynamic Therapy (PDT) |

Arm description:

Subjects received 2 milligram (mg) [0.05 millilitre (mL)] aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 milligram per millilitre [mg/mL] of 5 percent [%] dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Aflibercept      |
| Investigational medicinal product code | BAY86-5321       |
| Other name                             | Eylea            |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Intravitreal use |

Dosage and administration details:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally from Week 0 to Week 96.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Sham PDT               |
| Investigational medicinal product code |                        |
| Other name                             | Verteporfin, Visudyne  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Subjects received sham PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 96.

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | Aflibercept + Active PDT |
|------------------|--------------------------|

Arm description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of

aflibercept intravitreally with sham PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Aflibercept      |
| Investigational medicinal product code | BAY86-5321       |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Intravitreal use |

Dosage and administration details:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally from Week 0 to Week 96.

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | Active PDT             |
| Investigational medicinal product code |                        |
| Other name                             | Verteporfin, Visudyne  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravenous use        |

Dosage and administration details:

Subjects received active PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 96.

|                  |                              |
|------------------|------------------------------|
| <b>Arm title</b> | Aflibercept (Non-randomized) |
|------------------|------------------------------|

Arm description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 as run-in treatment, until the subjects were randomized and received rescue treatments.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Aflibercept      |
| Investigational medicinal product code | BAY86-5321       |
| Other name                             | Eylea            |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Intravitreal use |

Dosage and administration details:

Subjects received 3 injections of 2 mg (0.05 mL injected intravitreally) aflibercept in monthly intervals (Weeks 0, 4, and 8).

| Number of subjects in period 1 | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT | Aflibercept (Non-randomized) |
|--------------------------------|-----------------------------------------------|--------------------------|------------------------------|
|                                |                                               |                          |                              |
| Started                        | 157                                           | 161                      | 15                           |
| Completed                      | 137                                           | 147                      | 0                            |
| Not completed                  | 20                                            | 14                       | 15                           |
| Consent withdrawn by subject   | 6                                             | 3                        | 2                            |
| Adverse Event                  | 5                                             | 4                        | 3                            |
| Death                          | 3                                             | -                        | 1                            |
| Other                          | 5                                             | 4                        | 1                            |
| Lost to follow-up              | -                                             | 2                        | 1                            |
| Protocol deviation             | 1                                             | 1                        | 7                            |



## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                               |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Aflibercept + Sham Photodynamic Therapy (PDT) |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                               |
| Subjects received 2 milligram (mg) [0.05 millilitre (mL)] aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 milligram per millilitre [mg/mL] of 5 percent [%] dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96. |                                               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Aflibercept + Active PDT                      |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                               |
| Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.                                                                |                                               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Aflibercept (Non-randomized)                  |
| Reporting group description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                               |
| Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 as run-in treatment, until the subjects were randomized and received rescue treatments.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                               |

| Reporting group values                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT | Aflibercept (Non-randomized) |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|--------------------------|------------------------------|
| Number of subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 157                                           | 161                      | 15                           |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                               |                          |                              |
| Age continuous<br>Units: years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                               |                          |                              |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 70.8                                          | 70.4                     | 71.8                         |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | ± 8.4                                         | ± 8                      | ± 10.2                       |
| Gender categorical<br>Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                               |                          |                              |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 47                                            | 49                       | 8                            |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 110                                           | 112                      | 7                            |
| Baseline BCVA score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                               |                          |                              |
| Visual function of the study eye and fellow eye was assessed at each study visit according to the standard procedure developed for the ETDRS adapted for AREDS, using 70 letter charts at a starting distance of 4 meters. Participants were challenged with reading letters on lines of an eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until they reached a row where a minimum of three letters on a line could be read, and were scored by how many letters could be correctly identified. |                                               |                          |                              |
| Units: Letters                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                               |                          |                              |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 57.7                                          | 59.0                     | 61.8                         |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | ± 11.3                                        | ± 11.5                   | ± 15.2                       |
| Central Subfield Thickness                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                               |                          |                              |

|                    |         |         |         |
|--------------------|---------|---------|---------|
| Units: Micrometer  |         |         |         |
| arithmetic mean    | 347.8   | 346.1   | 325.8   |
| standard deviation | ± 118.9 | ± 117.5 | ± 117.9 |

|                               |       |  |  |
|-------------------------------|-------|--|--|
| <b>Reporting group values</b> | Total |  |  |
| Number of subjects            | 333   |  |  |
| Age categorical               |       |  |  |
| Units: Subjects               |       |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |  |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|--|--|
| Age continuous                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |  |  |
| Units: years                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |     |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |  |  |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -   |  |  |
| Gender categorical                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |     |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |  |  |
| Female                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 104 |  |  |
| Male                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 229 |  |  |
| Baseline BCVA score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |     |  |  |
| Visual function of the study eye and fellow eye was assessed at each study visit according to the standard procedure developed for the ETDRS adapted for AREDS, using 70 letter charts at a starting distance of 4 meters. Participants were challenged with reading letters on lines of an eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until they reached a row where a minimum of three letters on a line could be read, and were scored by how many letters could be correctly identified. |     |  |  |
| Units: Letters                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |     |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |  |  |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -   |  |  |
| Central Subfield Thickness                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |     |  |  |
| Units: Micrometer                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |     |  |  |
| arithmetic mean                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |     |  |  |
| standard deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | -   |  |  |



## End points

### End points reporting groups

|                       |                                               |
|-----------------------|-----------------------------------------------|
| Reporting group title | Aflibercept + Sham Photodynamic Therapy (PDT) |
|-----------------------|-----------------------------------------------|

#### Reporting group description:

Subjects received 2 milligram (mg) [0.05 millilitre (mL)] aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 milligram per millilitre [mg/mL] of 5 percent [%] dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Aflibercept + Active PDT |
|-----------------------|--------------------------|

#### Reporting group description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 (run-in treatment); subjects were randomized on Week 12 and assessed for the rescue treatment (until the visual and anatomical outcomes allowed extension of the treatment interval) and then subjects received either bi-monthly injections of aflibercept intravitreally or bi-monthly injections of aflibercept intravitreally with sham PDT (2 mg/mL of 5% dextrose solution or physiological saline solution), from Week 16 to Week 52. After week 52, treat-and-extend visit were scheduled and evaluation of rescue were continued with an optional extension treatment phase, where subjects received intravitreally injections of aflibercept monthly and sham PDT intravenously up to Week 96.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Aflibercept (Non-randomized) |
|-----------------------|------------------------------|

#### Reporting group description:

Subjects received 2 mg (0.05 mL) aflibercept injection intravitreally in monthly intervals on Weeks 0, 4, and 8 as run-in treatment, until the subjects were randomized and received rescue treatments.

|                            |                           |
|----------------------------|---------------------------|
| Subject analysis set title | Safety Analysis Set (SAF) |
|----------------------------|---------------------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

#### Subject analysis set description:

SAF (N=333) included all subjects who received any study drug under this protocol.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
|----------------------------|-------------------------|

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

#### Subject analysis set description:

FAS (N=318) included all randomized subjects.

### **Primary: Mean change in Best Corrected Visual Acuity (BCVA) as measured by Early Treatment of Diabetic Retinopathy Study (ETDRS) letter scores from baseline to Week 52 - Last observation carried forward (LOCF)**

|                 |                                                                                                                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Mean change in Best Corrected Visual Acuity (BCVA) as measured by Early Treatment of Diabetic Retinopathy Study (ETDRS) letter scores from baseline to Week 52 - Last observation carried forward (LOCF) <sup>[1]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

Visual function of the study eye and fellow eye was assessed at each study visit according to the standard procedure developed for the ETDRS adapted for Age Related Eye Disease Study (AREDS), using 70 letter charts at a starting distance of 4 meters. Participants were challenged with reading letters on lines of an eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until they reached a row where a minimum of three letters on a line could be read, and were scored by how many letters could be correctly identified.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

#### End point timeframe:

From Baseline to Week 52

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values                     | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed          | 157 <sup>[2]</sup>                            | 161 <sup>[3]</sup>       |  |  |
| Units: Letters correctly read        |                                               |                          |  |  |
| arithmetic mean (standard deviation) | 10.7 ( $\pm$ 11.3)                            | 10.8 ( $\pm$ 10.7)       |  |  |

Notes:

[2] - FAS

[3] - FAS

## Statistical analyses

| Statistical analysis title              | Statistical Analysis                                                     |
|-----------------------------------------|--------------------------------------------------------------------------|
| Comparison groups                       | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
| Number of subjects included in analysis | 318                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.548                                                                  |
| Method                                  | ANCOVA                                                                   |
| Parameter estimate                      | Mean difference (net)                                                    |
| Point estimate                          | -0.7                                                                     |
| Confidence interval                     |                                                                          |
| level                                   | 95 %                                                                     |
| sides                                   | 2-sided                                                                  |
| lower limit                             | -2.9                                                                     |
| upper limit                             | 1.6                                                                      |

## Secondary: Percentage of Subjects Who Avoided at Least 15 Letters Loss in Early Treatment of Diabetic Retinopathy Study (ETDRS) From Baseline to Week 52

|                 |                                                                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects Who Avoided at Least 15 Letters Loss in Early Treatment of Diabetic Retinopathy Study (ETDRS) From Baseline to Week 52 <sup>[4]</sup> |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Visual function of the study eye and fellow eye was assessed at each study visit according to the standard procedure developed for the ETDRS adapted for Age Related Eye Disease Study (AREDS), using 70 letter charts at a starting distance of 4 meters. Participants were challenged with reading letters on lines of an eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until they reached a row where a minimum of three letters on a line could be read, and were scored by how many letters could be correctly identified.

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

End point timeframe:

Baseline up to week 52

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values              | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|-------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type            | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed   | 157                                           | 161                      |  |  |
| Units: percentage of subjects |                                               |                          |  |  |
| number (not applicable)       | 97.5                                          | 96.9                     |  |  |

## Statistical analyses

| Statistical analysis title              | Statistical analysis 1                                                   |
|-----------------------------------------|--------------------------------------------------------------------------|
| Comparison groups                       | Aflibercept + Active PDT v Aflibercept + Sham Photodynamic Therapy (PDT) |
| Number of subjects included in analysis | 318                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.7402                                                                 |
| Method                                  | Cochran-Mantel-Haenszel                                                  |
| Parameter estimate                      | Treatment difference                                                     |
| Point estimate                          | 0.6                                                                      |
| Confidence interval                     |                                                                          |
| level                                   | 95 %                                                                     |
| sides                                   | 2-sided                                                                  |
| lower limit                             | -3.1                                                                     |
| upper limit                             | 4.3                                                                      |

## Other pre-specified: Percentage of subjects who never need rescue therapy in the first year

|                        |                                                                                       |
|------------------------|---------------------------------------------------------------------------------------|
| End point title        | Percentage of subjects who never need rescue therapy in the first year <sup>[5]</sup> |
| End point description: |                                                                                       |
| End point type         | Other pre-specified                                                                   |
| End point timeframe:   |                                                                                       |
| Baseline to Week 52    |                                                                                       |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values              | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|-------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type            | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed   | 157                                           | 161                      |  |  |
| Units: Percentage of subjects |                                               |                          |  |  |
| number (not applicable)       | 87.9                                          | 85.7                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of PDT treatments in the study eye before Week 52

|                 |                                                                         |
|-----------------|-------------------------------------------------------------------------|
| End point title | Number of PDT treatments in the study eye before Week 52 <sup>[6]</sup> |
|-----------------|-------------------------------------------------------------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 52

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values                     | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed          | 157                                           | 161                      |  |  |
| Units: PDT administrations           |                                               |                          |  |  |
| arithmetic mean (standard deviation) | 0.2 (± 0.7)                                   | 0.2 (± 0.4)              |  |  |

### Statistical analyses

|                                         |                                                                          |
|-----------------------------------------|--------------------------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 1                                                   |
| Comparison groups                       | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
| Number of subjects included in analysis | 318                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.0682                                                                 |
| Method                                  | ANCOVA                                                                   |
| Parameter estimate                      | LS mean difference                                                       |

|                     |      |
|---------------------|------|
| Confidence interval |      |
| level               | 95 % |

### Other pre-specified: Number of aflibercept treatments in the study eye (after randomization) before Week 52

|                 |                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------|
| End point title | Number of aflibercept treatments in the study eye (after randomization) before Week 52 <sup>[7]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 52

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values                     | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed          | 154                                           | 160 <sup>[8]</sup>       |  |  |
| Units: Aflibercept injections        |                                               |                          |  |  |
| arithmetic mean (standard deviation) | 5.2 (± 1.1)                                   | 5.1 (± 0.8)              |  |  |

Notes:

[8] - FAS with evaluable subjects for this outcome measure

### Statistical analyses

|                                         |                                                                          |
|-----------------------------------------|--------------------------------------------------------------------------|
| Statistical analysis title              | Statistical analysis 1                                                   |
| Comparison groups                       | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
| Number of subjects included in analysis | 314                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.164                                                                  |
| Method                                  | ANCOVA                                                                   |
| Parameter estimate                      | LS mean difference                                                       |
| Point estimate                          | 0.164                                                                    |
| Confidence interval                     |                                                                          |
| level                                   | 95 %                                                                     |
| sides                                   | 2-sided                                                                  |
| lower limit                             | -0.1                                                                     |
| upper limit                             | 0.3                                                                      |

### Other pre-specified: Time to first administration of PDT in the study eye before Week 52

|                        |                                                                                    |
|------------------------|------------------------------------------------------------------------------------|
| End point title        | Time to first administration of PDT in the study eye before Week 52 <sup>[9]</sup> |
| End point description: |                                                                                    |
| End point type         | Other pre-specified                                                                |
| End point timeframe:   |                                                                                    |
| Baseline to Week 52    |                                                                                    |

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values                       | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|----------------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type                     | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed            | 157                                           | 161                      |  |  |
| Units: Days                            |                                               |                          |  |  |
| arithmetic mean (full range (min-max)) | 131.2 (80 to 278)                             | 128.2 (80 to 315)        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Change of visual acuity (letters) from baseline over time (week) in the study eye

|                        |                                                                                                   |
|------------------------|---------------------------------------------------------------------------------------------------|
| End point title        | Change of visual acuity (letters) from baseline over time (week) in the study eye <sup>[10]</sup> |
| End point description: |                                                                                                   |
| End point type         | Other pre-specified                                                                               |
| End point timeframe:   |                                                                                                   |
| Baseline to Week 52    |                                                                                                   |

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values                     | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed          | 157                                           | 161                      |  |  |
| Units: Letters                       |                                               |                          |  |  |
| arithmetic mean (standard deviation) | 10.7 (± 11.3)                                 | 10.8 (± 10.7)            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percentage of subjects who gained $\geq 5$ , 10, or 15 letters at Week 52

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Percentage of subjects who gained $\geq 5$ , 10, or 15 letters at Week 52 <sup>[11]</sup> |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 52

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values              | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|-------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type            | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed   | 157                                           | 161                      |  |  |
| Units: Percentage of subjects |                                               |                          |  |  |
| number (not applicable)       |                                               |                          |  |  |
| Gained $\geq 5$               | 73.9                                          | 78.9                     |  |  |
| Gained $\geq 10$              | 55.4                                          | 57.1                     |  |  |
| Gained $\geq 15$              | 33.1                                          | 36.6                     |  |  |

## Statistical analyses

|                            |                             |
|----------------------------|-----------------------------|
| Statistical analysis title | Category of Gained $\geq 5$ |
|----------------------------|-----------------------------|

Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

|                   |                                                                          |
|-------------------|--------------------------------------------------------------------------|
| Comparison groups | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
|-------------------|--------------------------------------------------------------------------|

|                                         |                           |
|-----------------------------------------|---------------------------|
| Number of subjects included in analysis | 318                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.2348                  |
| Method                                  | Cochran-Mantel-Haenszel   |
| Parameter estimate                      | treatment difference in % |
| Point estimate                          | -5.6                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | -14.9                     |
| upper limit                             | 3.7                       |

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Category of Gained $\geq 10$ |
|-----------------------------------|------------------------------|

Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

|                                         |                                                                          |
|-----------------------------------------|--------------------------------------------------------------------------|
| Comparison groups                       | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
| Number of subjects included in analysis | 318                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.6877                                                                 |
| Method                                  | Cochran-Mantel-Haenszel                                                  |
| Parameter estimate                      | treatment difference in %                                                |
| Point estimate                          | -2.2                                                                     |
| Confidence interval                     |                                                                          |
| level                                   | 95 %                                                                     |
| sides                                   | 2-sided                                                                  |
| lower limit                             | -13.1                                                                    |
| upper limit                             | 8.6                                                                      |

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Category of Gained $\geq 15$ |
|-----------------------------------|------------------------------|

Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

|                   |                                                                          |
|-------------------|--------------------------------------------------------------------------|
| Comparison groups | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
|-------------------|--------------------------------------------------------------------------|



|                                         |                           |
|-----------------------------------------|---------------------------|
| Number of subjects included in analysis | 318                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.4556                  |
| Method                                  | Cochran-Mantel-Haenszel   |
| Parameter estimate                      | treatment difference in % |
| Point estimate                          | -4                        |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | -14.5                     |
| upper limit                             | 6.5                       |

## Other pre-specified: Percentage of subjects who lost ≥5, 10, or 15 letters at Week 52

|                 |                                                                                  |
|-----------------|----------------------------------------------------------------------------------|
| End point title | Percentage of subjects who lost ≥5, 10, or 15 letters at Week 52 <sup>[12]</sup> |
|-----------------|----------------------------------------------------------------------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 52

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values              | Aflibercept + Sham<br>Photodynamic<br>Therapy (PDT) | Aflibercept +<br>Active PDT |  |  |
|-------------------------------|-----------------------------------------------------|-----------------------------|--|--|
| Subject group type            | Reporting group                                     | Reporting group             |  |  |
| Number of subjects analysed   | 157                                                 | 161                         |  |  |
| Units: Percentage of subjects |                                                     |                             |  |  |
| number (not applicable)       |                                                     |                             |  |  |
| Lost ≥ 5                      | 7.0                                                 | 5.6                         |  |  |
| Lost ≥ 10                     | 3.8                                                 | 3.1                         |  |  |
| Lost ≥ 15                     | 2.5                                                 | 3.1                         |  |  |

## Statistical analyses

|                            |                      |
|----------------------------|----------------------|
| Statistical analysis title | Category of Lost ≥ 5 |
|----------------------------|----------------------|

Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

|                                         |                                                                          |
|-----------------------------------------|--------------------------------------------------------------------------|
| Comparison groups                       | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
| Number of subjects included in analysis | 318                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.5372                                                                 |
| Method                                  | Cochran-Mantel-Haenszel                                                  |
| Parameter estimate                      | treatment difference in %                                                |
| Point estimate                          | 1.7                                                                      |
| Confidence interval                     |                                                                          |
| level                                   | 95 %                                                                     |
| sides                                   | 2-sided                                                                  |
| lower limit                             | -3.7                                                                     |
| upper limit                             | 7.2                                                                      |

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Category of Lost $\geq 10$ |
|-----------------------------------|----------------------------|

Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

|                                         |                                                                          |
|-----------------------------------------|--------------------------------------------------------------------------|
| Comparison groups                       | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
| Number of subjects included in analysis | 318                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.7569                                                                 |
| Method                                  | Cochran-Mantel-Haenszel                                                  |
| Parameter estimate                      | treatment difference in %                                                |
| Point estimate                          | 0.6                                                                      |
| Confidence interval                     |                                                                          |
| level                                   | 95 %                                                                     |
| sides                                   | 2-sided                                                                  |
| lower limit                             | -3.4                                                                     |
| upper limit                             | 4.7                                                                      |

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | Category of Lost $\geq 15$ |
|-----------------------------------|----------------------------|

Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

|                   |                                                                          |
|-------------------|--------------------------------------------------------------------------|
| Comparison groups | Aflibercept + Active PDT v Aflibercept + Sham Photodynamic Therapy (PDT) |
|-------------------|--------------------------------------------------------------------------|

|                                         |                           |
|-----------------------------------------|---------------------------|
| Number of subjects included in analysis | 318                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.7402                  |
| Method                                  | Cochran-Mantel-Haenszel   |
| Parameter estimate                      | treatment difference in % |
| Point estimate                          | -0.6                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | -4.3                      |
| upper limit                             | 3.1                       |

## Other pre-specified: Percentage of subjects with complete polyp regression at Week 52

|                 |                                                                                  |
|-----------------|----------------------------------------------------------------------------------|
| End point title | Percentage of subjects with complete polyp regression at Week 52 <sup>[13]</sup> |
|-----------------|----------------------------------------------------------------------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 52

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values              | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|-------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type            | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed   | 126 <sup>[14]</sup>                           | 134 <sup>[15]</sup>      |  |  |
| Units: Percentage of subjects |                                               |                          |  |  |
| number (not applicable)       | 38.9                                          | 44.8                     |  |  |

Notes:

[14] - FAS with evaluable subjects for this outcome measure.

[15] - FAS with evaluable subjects for this outcome measure.

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Statistical analysis title 1 |
|----------------------------|------------------------------|

Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

|                   |                                                                          |
|-------------------|--------------------------------------------------------------------------|
| Comparison groups | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
|-------------------|--------------------------------------------------------------------------|

|                                         |                           |
|-----------------------------------------|---------------------------|
| Number of subjects included in analysis | 260                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.3244                  |
| Method                                  | Cochran-Mantel-Haenszel   |
| Parameter estimate                      | treatment difference in % |
| Point estimate                          | -6                        |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | -17.8                     |
| upper limit                             | 5.9                       |

### Other pre-specified: Change of leakage area in Fluorescein angiography (FA) in the study eye at Week 52

|                 |                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------|
| End point title | Change of leakage area in Fluorescein angiography (FA) in the study eye at Week 52 <sup>[16]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------|

End point description:

Leakage is the release of fluorescein dye from diseased retinal vessels. Leakage area is defined as the area showing presence of fluorescein dye in the late stages of fluorescein angiography.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 52

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values                     | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed          | 140 <sup>[17]</sup>                           | 149 <sup>[18]</sup>      |  |  |
| Units: Square millimeter             |                                               |                          |  |  |
| arithmetic mean (standard deviation) | -1.3 (± 3.6)                                  | -1.2 (± 3.7)             |  |  |

Notes:

[17] - FAS with evaluable subjects for this outcome measure.

[18] - FAS with evaluable subjects for this outcome measure.

### Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Statistical analysis title 1 |
|----------------------------|------------------------------|

Statistical analysis description:

The analysis population included only subjects with leakage in FA at baseline and Week 52. Baseline values were not carried forward.

Point estimate, 95% CI and p-value are based on difference (AFL-sham – AFL-PDT) of LS mean changes using an ANCOVA model with treatment group and ethnicity and qualification for rescue therapy at Week 12 as fixed effects, baseline value as covariate.

|                   |                                                             |
|-------------------|-------------------------------------------------------------|
| Comparison groups | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept |
|-------------------|-------------------------------------------------------------|

|                                         |                    |
|-----------------------------------------|--------------------|
|                                         | + Active PDT       |
| Number of subjects included in analysis | 289                |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | other              |
| P-value                                 | = 0.7109           |
| Method                                  | ANCOVA             |
| Parameter estimate                      | LS mean difference |
| Point estimate                          | -0.1               |
| Confidence interval                     |                    |
| level                                   | 95 %               |
| sides                                   | 2-sided            |
| lower limit                             | -0.9               |
| upper limit                             | 0.6                |

### Other pre-specified: Change of Central subfield thickness (CST) on Optical coherence tomography (OCT) from baseline to Week 52

|                 |                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Change of Central subfield thickness (CST) on Optical coherence tomography (OCT) from baseline to Week 52 <sup>[19]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|

End point description:

Retinal and lesion characteristics, such as central retinal thickness (CRT), were evaluated by OCT in both eyes at every study visit. CRT was measured using optical coherence tomography to determine the average thickness of the retina in a circle with 1 millimeter of diameter centered on the fovea. This value is reported by some OCT devices as central subfield thickness (CST).

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 52

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values                     | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed          | 136 <sup>[20]</sup>                           | 150 <sup>[21]</sup>      |  |  |
| Units: millimeter(s)                 |                                               |                          |  |  |
| arithmetic mean (standard deviation) | -137.7 (± 116.0)                              | -143.5 (± 110.5)         |  |  |

Notes:

[20] - FAS with evaluable subjects for this outcome measure

[21] - FAS with evaluable subjects for this outcome measure

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The analysis population included only subjects with values for CST at baseline and Week 52. Baseline values were not carried forward.

Point estimate, 95% CI and p-value are based on difference (AFL-sham – AFL-PDT) of LS mean changes using an ANCOVA model with treatment group and ethnicity and qualification for rescue therapy at Week

12 as fixed effects, baseline value as covariate.

|                                         |                                                                          |
|-----------------------------------------|--------------------------------------------------------------------------|
| Comparison groups                       | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
| Number of subjects included in analysis | 286                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.8355                                                                 |
| Method                                  | ANCOVA                                                                   |
| Parameter estimate                      | LS mean difference                                                       |
| Point estimate                          | 1.1                                                                      |
| Confidence interval                     |                                                                          |
| level                                   | 95 %                                                                     |
| sides                                   | 2-sided                                                                  |
| lower limit                             | -9.2                                                                     |
| upper limit                             | 11.3                                                                     |

### Other pre-specified: Change in National Eye Institute 25-item visual function questionnaire (NEI VFQ-25) total score from baseline to Week 52

|                 |                                                                                                                                          |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change in National Eye Institute 25-item visual function questionnaire (NEI VFQ-25) total score from baseline to Week 52 <sup>[22]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The NEI VFQ-25 total score ranges from 0-100 with a score of 0 being the worst outcome and 100 being the best outcome. The NEI VFQ questionnaire is organized as a collection of subscales which are all scored from 0-100. To reach the overall composite score, each sub-scale score is averaged in order to give each sub-scale equal weight.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline to Week 52

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values                     | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|--------------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type                   | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed          | 143 <sup>[23]</sup>                           | 153 <sup>[24]</sup>      |  |  |
| Units: Scores on a scale             |                                               |                          |  |  |
| arithmetic mean (standard deviation) | 4.7 (± 10.3)                                  | 7.3 (± 12.5)             |  |  |

Notes:

[23] - FAS with evaluable subjects for this outcome measure.

[24] - FAS with evaluable subjects for this outcome measure.

### Statistical analyses

|                            |                                                             |
|----------------------------|-------------------------------------------------------------|
| Statistical analysis title | Statistical analysis 1                                      |
| Comparison groups          | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept |

|                                         |                    |
|-----------------------------------------|--------------------|
|                                         | + Active PDT       |
| Number of subjects included in analysis | 296                |
| Analysis specification                  | Pre-specified      |
| Analysis type                           | other              |
| P-value                                 | = 0.5069           |
| Method                                  | ANCOVA             |
| Parameter estimate                      | LS mean difference |
| Point estimate                          | -0.7               |
| Confidence interval                     |                    |
| level                                   | 95 %               |
| sides                                   | 2-sided            |
| lower limit                             | -2.9               |
| upper limit                             | 1.4                |

### Other pre-specified: Percentage of subjects for whom rescue therapy is indicated over the course till Week 52

|                 |                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------|
| End point title | Percentage of subjects for whom rescue therapy is indicated over the course till Week 52 <sup>[25]</sup> |
|-----------------|----------------------------------------------------------------------------------------------------------|

#### End point description:

Evaluations for qualification for rescue were conducted at each visit from Week 12 to Week 52.

Intensified aflibercept treatment plus active or sham PDT treatments were given at any of these visits if treatment criteria were met. Qualification for rescue was based upon insufficient gain of BCVA, leakage, and presence of active polyps.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

#### End point timeframe:

Baseline to Week 52

#### Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint reports only the data for the randomized subjects (N=318), excluding the non-randomized reporting group.

| End point values              | Aflibercept + Sham Photodynamic Therapy (PDT) | Aflibercept + Active PDT |  |  |
|-------------------------------|-----------------------------------------------|--------------------------|--|--|
| Subject group type            | Reporting group                               | Reporting group          |  |  |
| Number of subjects analysed   | 157                                           | 161                      |  |  |
| Units: Percentage of subjects |                                               |                          |  |  |
| number (not applicable)       | 12.1                                          | 14.3                     |  |  |

### Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

#### Statistical analysis description:

The p-value is calculated from the 2-sided Cochran-Mantel-Haenszel test adjusted by ethnicity and qualification for rescue therapy at Week 12.

CI is based on the treatment difference in % (AFL-sham – AFL-PDT) using the Mantel-Haenszel weighting scheme adjusted by ethnicity and qualification for rescue therapy at Week 12.

|                                         |                                                                          |
|-----------------------------------------|--------------------------------------------------------------------------|
| Comparison groups                       | Aflibercept + Sham Photodynamic Therapy (PDT) v Aflibercept + Active PDT |
| Number of subjects included in analysis | 318                                                                      |
| Analysis specification                  | Pre-specified                                                            |
| Analysis type                           | other                                                                    |
| P-value                                 | = 0.8423                                                                 |
| Method                                  | Cochran-Mantel-Haenszel                                                  |
| Parameter estimate                      | Difference %                                                             |
| Point estimate                          | -0.6                                                                     |
| Confidence interval                     |                                                                          |
| level                                   | 95 %                                                                     |
| sides                                   | 2-sided                                                                  |
| lower limit                             | -6.3                                                                     |
| upper limit                             | 5.1                                                                      |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 30 days after the last treatment. Approximately 100 weeks.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.0 |
|--------------------|------|

### Reporting groups

|                       |                        |
|-----------------------|------------------------|
| Reporting group title | Aflibercept + Sham PDT |
|-----------------------|------------------------|

Reporting group description:

Subjects received 2 milligram (mg) Intravitreal aflibercept injection (IAI) (Eylea, VEGF Trap-Eye, BAY86-5321) every month for the first 3 months (run-in period). At Week 12, subjects were assessed for the rescue treatment and randomized to receive Aflibercept injection plus sham photodynamic therapy (only in subjects qualifying for rescue therapy) until Week 52. Between Week 52 and Week 96, the treatment interval could have been extended (typically in increments of 1 or 2 weeks) at the discretion of the investigator when the visual and anatomic outcomes allowed.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Aflibercept + Active PDT |
|-----------------------|--------------------------|

Reporting group description:

Subjects received 2 mg Intravitreal aflibercept injection (IAI) (Eylea, VEGF Trap-Eye, BAY86-5321) every month for the first 3 months (run-in period). At Week 12, subjects were assessed for the rescue treatment and randomized to receive Aflibercept injection plus active photodynamic therapy (only in subjects qualifying for rescue therapy) until Week 52. Between Week 52 and Week 96, the treatment interval could have been extended (typically in increments of 1 or 2 weeks) at the discretion of the investigator when the visual and anatomic outcomes allowed.

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Aflibercept (Non-randomized) |
|-----------------------|------------------------------|

Reporting group description:

Subjects received 2 mg Intravitreal aflibercept injection (IAI) (Eylea, VEGF Trap-Eye, BAY86-5321) every month for the first 3 months (run-in period), but discontinued study participation before randomization.

| Serious adverse events                                              | Aflibercept + Sham PDT | Aflibercept + Active PDT | Aflibercept (Non-randomized) |
|---------------------------------------------------------------------|------------------------|--------------------------|------------------------------|
| Total subjects affected by serious adverse events                   |                        |                          |                              |
| subjects affected / exposed                                         | 27 / 157 (17.20%)      | 25 / 161 (15.53%)        | 4 / 15 (26.67%)              |
| number of deaths (all causes)                                       | 3                      | 0                        | 1                            |
| number of deaths resulting from adverse events                      | 1                      | 0                        | 1                            |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                        |                          |                              |
| Acoustic neuroma                                                    |                        |                          |                              |
| subjects affected / exposed                                         | 0 / 157 (0.00%)        | 0 / 161 (0.00%)          | 1 / 15 (6.67%)               |
| occurrences causally related to treatment / all                     | 0 / 0                  | 0 / 0                    | 0 / 1                        |
| deaths causally related to treatment / all                          | 0 / 0                  | 0 / 0                    | 0 / 0                        |
| Adenocarcinoma gastric                                              |                        |                          |                              |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Colon cancer                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastric cancer                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Metastases to lung                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Neoplasm                                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Thyroid neoplasm                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lung neoplasm malignant                         |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastric adenoma                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Prostate cancer                                 |                 |                 |                |

|                                                      |                 |                 |                |
|------------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                          | 1 / 157 (0.64%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Vascular disorders                                   |                 |                 |                |
| Varicose vein                                        |                 |                 |                |
| subjects affected / exposed                          | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Surgical and medical procedures                      |                 |                 |                |
| Transcatheter arterial chemoembolisation             |                 |                 |                |
| subjects affected / exposed                          | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                 |                 |                |
| Death                                                |                 |                 |                |
| subjects affected / exposed                          | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 0          |
| Sudden cardiac death                                 |                 |                 |                |
| subjects affected / exposed                          | 0 / 157 (0.00%) | 0 / 161 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 1 / 1          |
| Reproductive system and breast disorders             |                 |                 |                |
| Benign prostatic hyperplasia                         |                 |                 |                |
| subjects affected / exposed                          | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Cystocele                                            |                 |                 |                |
| subjects affected / exposed                          | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                |
| Acute pulmonary oedema                               |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Chronic obstructive pulmonary disease           |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 13          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Dyspnoea                                        |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Injury, poisoning and procedural complications  |                 |                 |                |
| Animal bite                                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Fall                                            |                 |                 |                |
| subjects affected / exposed                     | 2 / 157 (1.27%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Head injury                                     |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Femoral neck fracture                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hip fracture                                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Joint dislocation                               |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Radius fracture                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Rib fracture                                    |                 |                 |                |
| subjects affected / exposed                     | 2 / 157 (1.27%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Subdural haematoma                              |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Scapula fracture                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Afferent loop syndrome                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lumbar vertebral fracture                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Traumatic haemothorax                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac disorders                               |                 |                 |                |
| Angina pectoris                                 |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Angina unstable                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Arrhythmia                                      |                 |                 |                |
| subjects affected / exposed                     | 2 / 157 (1.27%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Cardiac failure congestive                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Coronary artery stenosis                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Stress cardiomyopathy                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Nervous system disorders                        |                 |                 |                |
| Senile dementia                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 161 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Eye disorders                                   |                 |                 |                |
| Cataract                                        |                 |                 |                |
| subjects affected / exposed                     | 2 / 157 (1.27%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Retinal artery occlusion                        |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Eyelid ptosis                                   |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Retinal haemorrhage                             |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Visual acuity reduced                           |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 2 / 161 (1.24%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Retinal pigment epithelial tear                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 0 / 161 (0.00%) | 1 / 15 (6.67%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Gastrointestinal disorders                      |                 |                 |                |
| Ileus                                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Inguinal hernia                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Large intestine perforation                     |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Upper gastrointestinal haemorrhage              |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Large intestine polyp                           |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Inguinal hernia strangulated                    |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Hepatobiliary disorders                         |                 |                 |                |
| Bile duct stone                                 |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Skin and subcutaneous tissue disorders          |                 |                 |                |
| Erythema                                        |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Renal and urinary disorders                     |                 |                 |                |
| Ureterolithiasis                                |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Haematuria                                      |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                 |                 |                |
| Cervical spinal stenosis                        |                 |                 |                |



|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Exostosis                                       |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Lumbar spinal stenosis                          |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Osteonecrosis                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Osteoarthritis                                  |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Infections and infestations                     |                 |                 |                |
| Ear infection                                   |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Endophthalmitis                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Pneumonia                                       |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 3 / 161 (1.86%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Septic shock                                    |                 |                 |                |

|                                                 |                 |                 |                |
|-------------------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Upper respiratory tract infection               |                 |                 |                |
| subjects affected / exposed                     | 0 / 157 (0.00%) | 1 / 161 (0.62%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |
| Metabolism and nutrition disorders              |                 |                 |                |
| Iron deficiency                                 |                 |                 |                |
| subjects affected / exposed                     | 1 / 157 (0.64%) | 0 / 161 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Aflibercept + Sham PDT | Aflibercept + Active PDT | Aflibercept (Non-randomized) |
|-------------------------------------------------------|------------------------|--------------------------|------------------------------|
| Total subjects affected by non-serious adverse events |                        |                          |                              |
| subjects affected / exposed                           | 59 / 157 (37.58%)      | 49 / 161 (30.43%)        | 3 / 15 (20.00%)              |
| Investigations                                        |                        |                          |                              |
| Intraocular pressure increased                        |                        |                          |                              |
| subjects affected / exposed                           | 6 / 157 (3.82%)        | 9 / 161 (5.59%)          | 0 / 15 (0.00%)               |
| occurrences (all)                                     | 18                     | 20                       | 0                            |
| Vascular disorders                                    |                        |                          |                              |
| Hypertension                                          |                        |                          |                              |
| subjects affected / exposed                           | 6 / 157 (3.82%)        | 13 / 161 (8.07%)         | 2 / 15 (13.33%)              |
| occurrences (all)                                     | 6                      | 13                       | 2                            |
| Eye disorders                                         |                        |                          |                              |
| Dry eye                                               |                        |                          |                              |
| subjects affected / exposed                           | 6 / 157 (3.82%)        | 11 / 161 (6.83%)         | 0 / 15 (0.00%)               |
| occurrences (all)                                     | 11                     | 22                       | 0                            |
| Conjunctival haemorrhage                              |                        |                          |                              |
| subjects affected / exposed                           | 10 / 157 (6.37%)       | 5 / 161 (3.11%)          | 0 / 15 (0.00%)               |
| occurrences (all)                                     | 31                     | 8                        | 0                            |
| Visual acuity reduced                                 |                        |                          |                              |

|                                                                                                                            |                         |                         |                     |
|----------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                                                           | 7 / 157 (4.46%)<br>7    | 9 / 161 (5.59%)<br>10   | 0 / 15 (0.00%)<br>0 |
| Ocular hypertension<br>subjects affected / exposed<br>occurrences (all)                                                    | 3 / 157 (1.91%)<br>4    | 1 / 161 (0.62%)<br>1    | 1 / 15 (6.67%)<br>1 |
| Retinal pigment epithelial tear<br>subjects affected / exposed<br>occurrences (all)                                        | 4 / 157 (2.55%)<br>4    | 0 / 161 (0.00%)<br>0    | 1 / 15 (6.67%)<br>1 |
| Vitreous floaters<br>subjects affected / exposed<br>occurrences (all)                                                      | 9 / 157 (5.73%)<br>10   | 1 / 161 (0.62%)<br>1    | 0 / 15 (0.00%)<br>0 |
| Psychiatric disorders<br>Depression<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 157 (0.64%)<br>1    | 0 / 161 (0.00%)<br>0    | 1 / 15 (6.67%)<br>1 |
| Infections and infestations<br>Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 25 / 157 (15.92%)<br>41 | 18 / 161 (11.18%)<br>25 | 0 / 15 (0.00%)<br>0 |

## 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.

|                                                                          |
|--------------------------------------------------------------------------|
| Decimal places were automatically truncated if last decimal equals zero. |
|--------------------------------------------------------------------------|

Notes: