



## Clinical trial results:

**A randomized, double masked, active controlled, phase III study of the efficacy and safety of repeated doses of intravitreal VEGF Trap-Eye in subjects with diabetic macular edema**

### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2010-022364-12       |
| Trial protocol           | DE AT CZ ES DK IT HU |
| Global end of trial date | 30 March 2015        |

### Results information

|                                |   |
|--------------------------------|---|
| Result version number          | v2 (current)  |
| This version publication date  | 04 September 2016   |
| First version publication date | 06 April 2016   |
| Version creation reason        | <ul style="list-style-type: none"><li>• New data added to full data set</li><li>• Correction of full data set</li></ul> Bayer sponsor contact information to be updated |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY86-5321/91745 |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01331681 |
| WHO universal trial number (UTN)   | -           |

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 |
| Scientific contact           | Therapeutic Area Head, 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                       | 30 March 2015 |
| Is this the analysis of the primary completion data? | No            |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 30 March 2015 |
| Was the trial ended prematurely?                     | No            |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the efficacy of intravitreal (IVT) administered vascular endothelial growth factor (VEGF) Trap-Eye in comparison to macular laser photocoagulation treatment in improving best corrected visual acuity (BCVA) in subjects with diabetic macular edema (DME).

Protection of trial subjects:

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                          | 09 May 2011 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Japan: 77          |
| Country: Number of subjects enrolled | Australia: 18      |
| Country: Number of subjects enrolled | Austria: 15        |
| Country: Number of subjects enrolled | Czech Republic: 39 |
| Country: Number of subjects enrolled | Germany: 52        |
| Country: Number of subjects enrolled | Denmark: 3         |
| Country: Number of subjects enrolled | Spain: 57          |
| Country: Number of subjects enrolled | France: 28         |
| Country: Number of subjects enrolled | Hungary: 76        |
| Country: Number of subjects enrolled | Italy: 27          |
| Country: Number of subjects enrolled | Poland: 14         |
| Worldwide total number of subjects   | 406                |
| EEA total number of subjects         | 311                |

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)                      | 214 |
| From 65 to 84 years                       | 192 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects with diabetic macular edema (DME) secondary to diabetes mellitus involving the center of the macula in the study eye could participate in the study. The study was conducted at 73 study centers in Japan, European Countries and Australia in subjects between 09 May 2011 (first subject first visit) and 30 Mar 2015 (last subject last visit).

### Pre-assignment

Screening details:

Of 604 subjects who were screened for inclusion in the study, 406 were randomized, and 404 received treatment.

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 406 |
| Number of subjects completed | 404 |

### Pre-assignment subject non-completion reasons

|                            |                                 |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Not Received Study Treatment: 2 |
|----------------------------|---------------------------------|

### Period 1

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

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes                                    |
| <b>Arm title</b>             | Intravitreal Aflibercept Injection 2Q4 |

Arm description:

Subjects received 2 milligram (mg) Intravitreal aflibercept injection (IAI) (EYLEA, vascular endothelial growth factor [VEGF] Trap-Eye, BAY86-5321) every 4 weeks (2Q4).

|  |  |
|--|--|
| Arm type                               | Experimental                           |
| Investigational medicinal product name | VEGF Trap-Eye                          |
| Investigational medicinal product code | BAY86-5321                             |
| Other name                             | Aflibercept and Eylea                  |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intravitreal use                       |

Dosage and administration details:

Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) 2Q4.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Intravitreal Aflibercept Injection 2Q8 |
|------------------|--|

Arm description:

Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections every 8 weeks (2Q8).

|  |  |
|--|--|
| Arm type                               | Experimental                           |
| Investigational medicinal product name | VEGF Trap-Eye                          |
| Investigational medicinal product code | BAY86-5321                             |
| Other name                             | Aflibercept and Eylea                  |
| Pharmaceutical forms                   | Concentrate for solution for injection |
| Routes of administration               | Intravitreal use                       |

**Dosage and administration details:**

Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections 2Q8.

|  |  |
|--|--|
| <b>Arm title</b>   | Macular Laser Photocoagulation (Control) |
| Arm description:<br>Subjects received laser treatment at baseline and as needed at visits at which laser re-treatment criteria were met, but no more frequently than every 12 weeks. During year 3 laser subjects could receive IAI as needed (PRN). |  |
| Arm type   | Procedure                                |
| No investigational medicinal product assigned in this arm  |  |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |
|---|--|--|--|
| Started   | 136                                    | 135                                    | 133                                      |
| Completed Week 52                                   | 125                                    | 121                                    | 115                                      |
| Completed Week 100                                  | 115                                    | 110                                    | 105                                      |
| Completed Week 148                                  | 101                                    | 101                                    | 100                                      |
| Completed   | 101                                    | 101                                    | 100                                      |
| Not completed                                       | 35                                     | 34                                     | 33                                       |
| Physician decision                                  | 2                                      | -                                      | 4  |
| Adverse Event                                       | 10                                     | 13                                     | 10                                       |
| Death   | 6                                      | 6                                      | 2  |
| Switching to other therapy                          | -                                      | -                                      | 1  |
| Withdrawal by Subject                               | 12                                     | 8                                      | 15                                       |
| Lost to follow-up                                   | 2                                      | 4                                      | 1  |
| Sponsor decision                                    | 1                                      | 1                                      | -  |
| Protocol deviation                                  | 1                                      | 1                                      | -  |
| Therapeutic procedure required                      | 1                                      | -                                      | -  |
| Lack of efficacy                                    | -                                      | 1                                      | -  |

**Notes:**

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

Justification: Worldwide number of subjects is equal to the number of subjects in the pre-assignment period and the baseline period starts with the number of subjects received the treatment.

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | Intravitreal Aflibercept Injection 2Q4   |
| Reporting group description:   |  |
| Subjects received 2 milligram (mg) Intravitreal aflibercept injection (IAI) (EYLEA, vascular endothelial growth factor [VEGF] Trap-Eye, BAY86-5321) every 4 weeks (2Q4).   |  |
| Reporting group title  | Intravitreal Aflibercept Injection 2Q8   |
| Reporting group description:   |  |
| Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections every 8 weeks (2Q8).   |  |
| Reporting group title  | Macular Laser Photocoagulation (Control) |
| Reporting group description:   |  |
| Subjects received laser treatment at baseline and as needed at visits at which laser re-treatment criteria were met, but no more frequently than every 12 weeks. During year 3 laser subjects could receive IAI as needed (PRN). |  |

| Reporting group values             | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |
|------------------------------------|--|--|--|
| Number of subjects                 | 136                                    | 135                                    | 133                                      |
| Age categorical<br>Units: Subjects |  |  |  |

|                    |       |       |       |
|--------------------|-------|-------|-------|
| Age continous      |       |       |       |
| Age continuous     |       |       |       |
| Units: years       |       |       |       |
| arithmetic mean    | 62.6  | 64.2  | 63.9  |
| standard deviation | ± 8.6 | ± 7.7 | ± 8.6 |
| Gender             |       |       |       |
| Units: subjects    |       |       |       |
| Female             | 53    | 47    | 54    |
| Male               | 83    | 88    | 79    |

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 404   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

|                    |     |  |  |
|--------------------|-----|--|--|
| Age continous      |     |  |  |
| Age continuous     |     |  |  |
| Units: years       |     |  |  |
| arithmetic mean    |     |  |  |
| standard deviation | -   |  |  |
| Gender             |     |  |  |
| Units: subjects    |     |  |  |
| Female             | 154 |  |  |
| Male               | 250 |  |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Intravitreal Aflibercept Injection 2Q4   |
| Reporting group description:<br>Subjects received 2 milligram (mg) Intravitreal aflibercept injection (IAI) (EYLEA, vascular endothelial growth factor [VEGF] Trap-Eye, BAY86-5321) every 4 weeks (2Q4).   |  |
| Reporting group title  | Intravitreal Aflibercept Injection 2Q8   |
| Reporting group description:<br>Subjects received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections every 8 weeks (2Q8).   |  |
| Reporting group title  | Macular Laser Photocoagulation (Control) |
| Reporting group description:<br>Subjects received laser treatment at baseline and as needed at visits at which laser re-treatment criteria were met, but no more frequently than every 12 weeks. During year 3 laser subjects could receive IAI as needed (PRN). |  |
| Subject analysis set title   | Safety analysis set (SAF)                |
| Subject analysis set type  | Safety analysis                          |
| Subject analysis set description:<br>SAF included all subjects who received at least 1 study treatment (active or sham). Treatment administration/compliance and all clinical safety and tolerability variables were analyzed using the SAF.                     |  |
| Subject analysis set title   | Full analysis set (FAS)                  |
| Subject analysis set type  | Full analysis                            |
| Subject analysis set description:<br>FAS included all randomized subjects who received any study treatment, had a baseline measurement of BCVA, and had at least 1 post-baseline assessment of BCVA. All efficacy endpoints were analyzed using the FAS.         |  |

### Primary: Change from Baseline in BCVA (Best Corrected Visual Acuity) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - Last Observation Carried Forward (LOCF)

|   |   |
|---|---|
| End point title   | Change from Baseline in BCVA (Best Corrected Visual Acuity) as Measured by Early Treatment Diabetic Retinopathy Study (ETDRS) Letter Score at Week 52 - Last Observation Carried Forward (LOCF) |
| End point description:<br>Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline up to Week 52  |   |

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 136 <sup>[1]</sup>                     | 135 <sup>[2]</sup>                     | 132 <sup>[3]</sup>                       |  |
| Units: letters correctly read        |  |  |  |  |
| arithmetic mean (standard deviation) | 10.5 (± 9.55)                          | 10.7 (± 9.32)                          | 1.2 (± 10.65)                            |  |

Notes:

[1] - FAS

[2] - FAS

[3] - FAS

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>                | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:                |   |
| Hypothesis: Mean change identical in both groups |   |
| Comparison groups                                | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis          | 268   |
| Analysis specification                           | Pre-specified   |
| Analysis type                                    | other <sup>[4]</sup>  |
| P-value  | < 0.0001 <sup>[5]</sup>   |
| Method   | ANCOVA  |
| Parameter estimate                               | Mean difference (final values)  |
| Point estimate                                   | 9.3   |
| Confidence interval                              |   |
| level  | Other: 97.5 %   |
| sides  | 2-sided   |
| lower limit                                      | 6.5   |
| upper limit                                      | 12  |

Notes:

[4] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. Least square (LS) mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[5] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value was below the significance level of 0.025, the fixed sequence testing did continue with the first secondary endpoint.

|  |   |
|--|---|
| <b>Statistical analysis title</b>                | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
| Statistical analysis description:                |   |
| Hypothesis: Mean change identical in both groups |   |
| Comparison groups                                | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis          | 267   |
| Analysis specification                           | Pre-specified   |
| Analysis type                                    | other <sup>[6]</sup>  |
| P-value  | < 0.0001 <sup>[7]</sup>   |
| Method   | ANCOVA  |
| Parameter estimate                               | Mean difference (final values)  |
| Point estimate                                   | 9.1   |
| Confidence interval                              |   |
| level  | Other: 97.5 %   |
| sides  | 2-sided   |
| lower limit                                      | 6.3   |
| upper limit                                      | 11.8  |

Notes:

[6] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.



[7] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value was below the significance level of 0.025, the fixed sequence testing did continue with the first secondary endpoint.

## Secondary: Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 52 - LOCF

|   |  |
|---|--|
| End point title   | Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 52 - LOCF |
| End point description:<br>Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. |  |
| End point type  | Secondary  |
| End point timeframe:<br>Baseline up to Week 52  |  |

| End point values              | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 136 <sup>[8]</sup>                     | 135 <sup>[9]</sup>                     | 132 <sup>[10]</sup>                      |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 54.4                                   | 53.3                                   | 25.8                                     |  |

Notes:

[8] - FAS

[9] - FAS

[10] - FAS

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:<br>Hypothesis: Probability to gain $\geq 10$ letters identical in both groups |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis   | 268   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[11]</sup>   |
| P-value   | $< 0.0001$ <sup>[12]</sup>  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 28.7  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 15.8  |
| upper limit   | 41.6  |

Notes:

[11] - stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[12] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value and

the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the second secondary endpoint.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
| Statistical analysis description:  |   |
| Hypothesis: Probability to gain $\geq 10$ letters identical in both groups |   |
| Comparison groups  | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                    | 267   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[13]</sup>   |
| P-value  | $< 0.0001$ <sup>[14]</sup>  |
| Method   | Cochran-Mantel-Haenszel   |
| Parameter estimate   | CMH adjusted difference   |
| Point estimate   | 27.5  |
| Confidence interval  |   |
| level  | Other: 97.5 %   |
| sides  | 2-sided   |
| lower limit  | 14.6  |
| upper limit  | 40.5  |

Notes:

[13] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[14] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the second secondary endpoint.

### **Secondary: Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 52 - LOCF**

|   |  |
|---|--|
| End point title   | Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 52 - LOCF |
| End point description:  |  |
| Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline up to Week 52  |  |

| <b>End point values</b>       | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 136 <sup>[15]</sup>                    | 135 <sup>[16]</sup>                    | 132 <sup>[17]</sup>                      |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 32.4                                   | 33.3                                   | 9.1                                      |  |

Notes:

[15] - FAS

[16] - FAS

[17] - FAS

## Statistical analyses

| Statistical analysis title   | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
|--|---|
| Statistical analysis description:  |   |
| Hypothesis: Probability to gain $\geq 15$ letters identical in both groups |   |
| Comparison groups  | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                    | 268   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[18]</sup>   |
| P-value  | $< 0.0001$ <sup>[19]</sup>  |
| Method   | Cochran-Mantel-Haenszel   |
| Parameter estimate   | CMH adjusted difference   |
| Point estimate   | 23.3  |
| Confidence interval  |   |
| level  | Other: 97.5 %   |
| sides  | 2-sided   |
| lower limit  | 12.6  |
| upper limit  | 33.9  |

Notes:

[18] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[19] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the third secondary endpoint.

| Statistical analysis title   | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
|--|---|
| Statistical analysis description:  |   |
| Hypothesis: Probability to gain $\geq 15$ letters identical in both groups |   |
| Comparison groups  | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                    | 267   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other <sup>[20]</sup>   |
| P-value  | $< 0.0001$ <sup>[21]</sup>  |
| Method   | Cochran-Mantel-Haenszel   |
| Parameter estimate   | CMH adjusted difference   |
| Point estimate   | 24.2  |
| Confidence interval  |   |
| level  | Other: 97.5 %   |
| sides  | 2-sided   |
| lower limit  | 13.5  |
| upper limit  | 34.9  |

Notes:

[20] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[21] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the third secondary endpoint.

### Secondary: Percentage of Subjects With a $\geq 2$ -Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 52 - LOCF

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With a $\geq 2$ -Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 52 - |
|-----------------|--|

End point description:

Baseline ETDRS DRSS: None (level 10); Mild to moderate nonproliferative DR (levels 14, 15, 20, 35, and 43); Moderately severe/severe nonproliferative DR (levels 47 and 53); Mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71, 75, 81, and 85)

End point type Secondary

End point timeframe:

Baseline up to Week 52

| End point values              | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 81 <sup>[22]</sup>                     | 83 <sup>[23]</sup>                     | 80 <sup>[24]</sup>                       |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 33.3                                   | 27.7                                   | 7.5                                      |  |

Notes:

[22] - FAS with assessment for this end-point.

[23] - FAS with assessment for this end-point.

[24] - FAS with assessment for this end-point.

## Statistical analyses

| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
|---|---|
| Statistical analysis description:   |   |
| Hypothesis: Probability to improve by $\geq 2$ steps identical in both groups |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                       | 161   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[25]</sup>   |
| P-value   | $< 0.0001$ <sup>[26]</sup>  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 25.8  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 12.2  |
| upper limit   | 39.4  |

Notes:

[25] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[26] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the fourth secondary endpoint.

| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
|---|---|
| Statistical analysis description:   |   |
| Hypothesis: Probability to improve by $\geq 2$ steps identical in both groups |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |

|   |                          |
|---|--------------------------|
| Number of subjects included in analysis | 163                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other <sup>[27]</sup>    |
| P-value                                 | = 0.0006 <sup>[28]</sup> |
| Method                                  | Cochran-Mantel-Haenszel  |
| Parameter estimate                      | CMH adjusted difference  |
| Point estimate                          | 19.3                     |
| Confidence interval                     |                          |
| level                                   | Other: 97.5 %            |
| sides                                   | 2-sided                  |
| lower limit                             | 6.6                      |
| upper limit                             | 32.1                     |

Notes:

[27] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[28] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the fourth secondary endpoint.

### Secondary: Change From Baseline in Central Retinal Thickness (CRT) at Week 52 as Assessed on Optical Coherence Tomography (OCT) - LOCF

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Central Retinal Thickness (CRT) at Week 52 as Assessed on Optical Coherence Tomography (OCT) - LOCF |
|-----------------|---|

End point description:

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

End point timeframe:

Baseline up to Week 52

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 135 <sup>[29]</sup>                    | 135 <sup>[30]</sup>                    | 132 <sup>[31]</sup>                      |  |
| Units: micrometer                    |  |  |  |  |
| arithmetic mean (standard deviation) | -195 ( $\pm$ 146.59)                   | -192.4 ( $\pm$ 149.89)                 | -66.2 ( $\pm$ 138.99)                    |  |

Notes:

[29] - FAS with assessment for this end-point.

[30] - FAS with assessment for this end-point.

[31] - FAS with assessment for this end-point.

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title                       | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:                |   |
| Hypothesis: Mean change identical in both groups |   |
| Comparison groups                                | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 267                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other <sup>[32]</sup>          |
| P-value                                 | < 0.0001 <sup>[33]</sup>       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -157                           |
| Confidence interval                     |                                |
| level                                   | Other: 97.5 %                  |
| sides                                   | 2-sided                        |
| lower limit                             | -190.9                         |
| upper limit                             | -123.1                         |

Notes:

[32] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[33] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the fifth secondary endpoint.

|  |   |
|--|---|
| <b>Statistical analysis title</b>                | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
| Statistical analysis description:                |   |
| Hypothesis: Mean change identical in both groups |   |
| Comparison groups                                | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis          | 267   |
| Analysis specification                           | Pre-specified   |
| Analysis type                                    | other <sup>[34]</sup>   |
| P-value  | < 0.0001 <sup>[35]</sup>  |
| Method   | ANCOVA  |
| Parameter estimate                               | Mean difference (final values)  |
| Point estimate                                   | -142.8  |
| Confidence interval                              |   |
| level  | Other: 97.5 %   |
| sides  | 2-sided   |
| lower limit                                      | -179.3  |
| upper limit                                      | -106.3  |

Notes:

[34] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

[35] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value and the preceding ones were below the significance level of 0.025, the fixed sequence testing did continue with the fifth secondary endpoint.

### **Secondary: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 52 - LOCF**

|  |  |
|--|--|
| End point title  | Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 52 - LOCF |
| 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 that are all scored from 0-100. Near activities are defined as reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf. |  |
| End point type   | Secondary  |

End point timeframe:  
Baseline up to Week 52

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 128 <sup>[36]</sup>                    | 134 <sup>[37]</sup>                    | 120 <sup>[38]</sup>                      |  |
| Units: scores on a scale             |  |  |  |  |
| arithmetic mean (standard deviation) | 5.73 ( $\pm$ 18.932)                   | 5.29 ( $\pm$ 19.058)                   | 3.54 ( $\pm$ 16.768)                     |  |

Notes:

[36] - FAS with assessment for this end-point.

[37] - FAS with assessment for this end-point.

[38] - FAS with assessment for this end-point.

## Statistical analyses

| Statistical analysis title                       | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
|--|---|
| Statistical analysis description:                |   |
| Hypothesis: Mean change identical in both groups |   |
| Comparison groups                                | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis          | 248   |
| Analysis specification                           | Pre-specified   |
| Analysis type                                    | other <sup>[39]</sup>   |
| P-value  | = 0.2208 <sup>[40]</sup>  |
| Method   | ANCOVA  |
| Parameter estimate                               | Mean difference (final values)  |
| Point estimate                                   | 2.41  |
| Confidence interval                              |   |
| level  | Other: 97.5 %   |
| sides  | 2-sided   |
| lower limit                                      | -2.01   |
| upper limit                                      | 6.82  |

Notes:

[39] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[40] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value is not below of 0.025, the fixed sequence testing stops here. The sixth secondary endpoint cannot be tested confirmatory.

| Statistical analysis title                       | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
|--|---|
| Statistical analysis description:                |   |
| Hypothesis: Mean change identical in both groups |   |
| Comparison groups                                | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 254                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other <sup>[41]</sup>          |
| P-value                                 | = 0.5537 <sup>[42]</sup>       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -1.21                          |
| Confidence interval                     |                                |
| level                                   | Other: 97.5 %                  |
| sides                                   | 2-sided                        |
| lower limit                             | -5.79                          |
| upper limit                             | 3.37                           |

Notes:

[41] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

[42] - Significance level  $\alpha=0.025$  for two sided test to adjust for multiplicity. Since this p-value is not below of 0.025, the fixed sequence testing stops here. The sixth secondary endpoint cannot be tested confirmatory.

### Secondary: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 52 - LOCF

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 52 - LOCF |
|-----------------|--|

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 that are all scored from 0-100. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs.

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

End point timeframe:

Baseline up to Week 52

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 128 <sup>[43]</sup>                    | 134 <sup>[44]</sup>                    | 120 <sup>[45]</sup>                      |  |
| Units: scores on a scale             |  |  |  |  |
| arithmetic mean (standard deviation) | 0.94 ( $\pm$ 16.487)                   | 5.32 ( $\pm$ 18.475)                   | 2.26 ( $\pm$ 15.923)                     |  |

Notes:

[43] - FAS with assessment for this end-point.

[44] - FAS with assessment for this end-point.

[45] - FAS with assessment for this end-point.

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title                       | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:                |   |
| Hypothesis: Mean change identical in both groups |   |
| Comparison groups                                | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 248                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other <sup>[46]</sup>          |
| P-value                                 | = 0.5138                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -1.19                          |
| Confidence interval                     |                                |
| level                                   | Other: 97.5 %                  |
| sides                                   | 2-sided                        |
| lower limit                             | -5.29                          |
| upper limit                             | 2.91                           |

Notes:

[46] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Intravitreal Aflibercept Injection 2Q8 vs. Control |
|-----------------------------------|--|

Statistical analysis description:

Hypothesis: Mean change identical in both groups

|   |   |
|---|---|
| Comparison groups                       | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis | 254   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[47]</sup>   |
| P-value                                 | = 0.8498  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | -0.37   |
| Confidence interval                     |   |
| level                                   | Other: 97.5 %   |
| sides                                   | 2-sided   |
| lower limit                             | -4.79   |
| upper limit                             | 4.05  |

Notes:

[47] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### **Other pre-specified: Change from Baseline in BCVA (best corrected visual acuity) as Measured by ETDRS Letter Score at Week 100 - LOCF**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in BCVA (best corrected visual acuity) as Measured by ETDRS Letter Score at Week 100 - LOCF |
|-----------------|--|

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.

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

End point timeframe:

Baseline up to Week 100

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 136 <sup>[48]</sup>                    | 135 <sup>[49]</sup>                    | 132 <sup>[50]</sup>                      |  |
| Units: letters correctly read        |  |  |  |  |
| arithmetic mean (standard deviation) | 11.4 (± 11.2)                          | 9.4 (± 10.5)                           | 0.7 (± 11.8)                             |  |

Notes:

[48] - FAS

[49] - FAS

[50] - FAS

## Statistical analyses

| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 268   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[51]</sup>   |
| P-value   | < 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | 10.7  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 7.6   |
| upper limit   | 13.8  |

Notes:

[51] - Stratifying by geographic region (Japan vs non-Japan). LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[52]</sup>   |
| P-value   | < 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | 8.2   |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 5.2   |
| upper limit   | 11.3  |

Notes:

[52] - Stratifying by geographic region (Japan vs non-Japan). LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### Other pre-specified: Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 100 - LOCF

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 100 - LOCF |
|-----------------|---|

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.

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

End point timeframe:

Baseline up to Week 100

| End point values              | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 136 <sup>[53]</sup>                    | 135 <sup>[54]</sup>                    | 132 <sup>[55]</sup>                      |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 58.1                                   | 49.6                                   | 25                                       |  |

Notes:

[53] - FAS

[54] - FAS

[55] - FAS

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Intravitreal Aflibercept Injection 2Q4 vs. Control |
|----------------------------|--|

Statistical analysis description:

These analysis are not confirmatory.

|                   |   |
|-------------------|---|
| Comparison groups | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
|-------------------|---|

|   |     |
|---|-----|
| Number of subjects included in analysis | 268 |
|---|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |                       |
|---------------|-----------------------|
| Analysis type | other <sup>[56]</sup> |
|---------------|-----------------------|

|         |          |
|---------|----------|
| P-value | < 0.0001 |
|---------|----------|

|        |                         |
|--------|-------------------------|
| Method | Cochran-Mantel-Haenszel |
|--------|-------------------------|

|                    |                         |
|--------------------|-------------------------|
| Parameter estimate | CMH adjusted difference |
|--------------------|-------------------------|

|                |      |
|----------------|------|
| Point estimate | 33.1 |
|----------------|------|

Confidence interval

|       |               |
|-------|---------------|
| level | Other: 97.5 % |
|-------|---------------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 20.3 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 45.9 |
|-------------|------|

Notes:

[56] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|                            |  |
|----------------------------|--|
| Statistical analysis title | Intravitreal Aflibercept Injection 2Q8 vs. Control |
|----------------------------|--|

|   |   |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[57]</sup>   |
| P-value   | < 0.0001  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 24.6  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 11.9  |
| upper limit   | 37.3  |

Notes:

[57] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### Other pre-specified: Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 100 - LOCF

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 100 - LOCF |
|-----------------|---|

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning.

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

End point timeframe:

Baseline up to Week 100

| End point values              | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 136 <sup>[58]</sup>                    | 135 <sup>[59]</sup>                    | 132 <sup>[60]</sup>                      |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 38.2                                   | 31.1                                   | 12.1                                     |  |

Notes:

[58] - FAS

[59] - FAS

[60] - FAS

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 268                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other <sup>[61]</sup>   |
| P-value                                 | < 0.0001                |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | CMH adjusted difference |
| Point estimate                          | 26.1                    |
| Confidence interval                     |                         |
| level                                   | Other: 97.5 %           |
| sides                                   | 2-sided                 |
| lower limit                             | 14.8                    |
| upper limit                             | 37.5                    |

Notes:

[61] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Intravitreal Aflibercept Injection 2Q8 vs. Control |
|-----------------------------------|--|

Statistical analysis description:

These analysis are not confirmatory.

|   |   |
|---|---|
| Comparison groups                       | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis | 267   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[62]</sup>   |
| P-value                                 | = 0.0001  |
| Method                                  | Cochran-Mantel-Haenszel   |
| Parameter estimate                      | CMH adjusted difference   |
| Point estimate                          | 19  |
| Confidence interval                     |   |
| level                                   | Other: 97.5 %   |
| sides                                   | 2-sided   |
| lower limit                             | 8   |
| upper limit                             | 29.9  |

Notes:

[62] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

**Other pre-specified: Percentage of Subjects with A  $\geq$  2-Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 100 - LOCF**

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects with A $\geq$ 2-Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 100 - LOCF |
|-----------------|---|

End point description:

Baseline ETDRS DRSS: None (level 10); Mild to moderate nonproliferative DR (levels 14, 15, 20, 35, and 43); Moderately severe/severe nonproliferative DR (levels 47 and 53); Mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71,75, 81, and 85)

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

End point timeframe:

Baseline up to Week 100

| End point values              | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 136 <sup>[63]</sup>                    | 135 <sup>[64]</sup>                    | 132 <sup>[65]</sup>                      |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 29.3                                   | 32.6                                   | 8.2                                      |  |

Notes:

[63] - FAS

[64] - FAS

[65] - FAS

## Statistical analyses

| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 268   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[66]</sup>   |
| P-value   | = 0.0004  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 20.9  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 7.7   |
| upper limit   | 34.2  |

Notes:

[66] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[67]</sup>   |
| P-value   | < 0.0001  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 24.4  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 11.3  |
| upper limit   | 37.4  |

Notes:

[67] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### Other pre-specified: Change from Baseline in Central Retinal Thickness (CRT) at Week 100 as Assessed on Optical Coherence Tomography (OCT) - LOCF

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Central Retinal Thickness (CRT) at Week 100 as Assessed on Optical Coherence Tomography (OCT) - LOCF |
|-----------------|--|

End point description:

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

End point timeframe:

Baseline up to Week 100

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 135 <sup>[68]</sup>                    | 135 <sup>[69]</sup>                    | 132 <sup>[70]</sup>                      |  |
| Units: micrometer                    |  |  |  |  |
| arithmetic mean (standard deviation) | -211.8 ( $\pm$ 150.9)                  | -195.8 ( $\pm$ 141.7)                  | -85.7 ( $\pm$ 145.8)                     |  |

Notes:

[68] - FAS

[69] - FAS

[70] - FAS

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Intravitreal Aflibercept Injection 2Q4 vs. Control |
|----------------------------|--|

Statistical analysis description:

These analysis are not confirmatory.

|                   |   |
|-------------------|---|
| Comparison groups | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
|-------------------|---|

|   |     |
|---|-----|
| Number of subjects included in analysis | 267 |
|---|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |                       |
|---------------|-----------------------|
| Analysis type | other <sup>[71]</sup> |
|---------------|-----------------------|

|         |          |
|---------|----------|
| P-value | < 0.0001 |
|---------|----------|

|        |        |
|--------|--------|
| Method | ANCOVA |
|--------|--------|

|                    |                                |
|--------------------|--------------------------------|
| Parameter estimate | Mean difference (final values) |
|--------------------|--------------------------------|

|                |        |
|----------------|--------|
| Point estimate | -154.4 |
|----------------|--------|

Confidence interval

|       |               |
|-------|---------------|
| level | Other: 97.5 % |
|-------|---------------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |        |
|-------------|--------|
| lower limit | -189.1 |
|-------------|--------|

|             |        |
|-------------|--------|
| upper limit | -119.7 |
|-------------|--------|

Notes:

[71] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[72]</sup>   |
| P-value   | < 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | -126.8  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | -164.6  |
| upper limit   | -89   |

Notes:

[72] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

#### **Other pre-specified: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 100 - LOCF**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 100 - LOCF |
|-----------------|---|

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 sub-scales that are all scored from 0-100. Near activities are defined as reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf.

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

End point timeframe:

Baseline up to Week 100

| <b>End point values</b>              | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 128 <sup>[73]</sup>                    | 134 <sup>[74]</sup>                    | 120 <sup>[75]</sup>                      |  |
| Units: scores on a scale             |  |  |  |  |
| arithmetic mean (standard deviation) | 8.2 (± 20.19)                          | 7 (± 19.28)                            | 4.8 (± 15.43)                            |  |

Notes:

[73] - FAS with assessment for this end-point.

[74] - FAS with assessment for this end-point.

[75] - FAS with assessment for this end-point.

#### **Statistical analyses**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Intravitreal Aflibercept Injection 2Q4 vs. Control |
|-----------------------------------|--|



Statistical analysis description:

These analysis are not confirmatory.

|   |   |
|---|---|
| Comparison groups                       | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis | 248   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[76]</sup>   |
| P-value                                 | = 0.0596  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | 3.64  |
| Confidence interval                     |   |
| level                                   | Other: 97.5 %   |
| sides                                   | 2-sided   |
| lower limit                             | -0.7  |
| upper limit                             | 7.98  |

Notes:

[76] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Intravitreal Aflibercept Injection 2Q8 vs. Control |
|-----------------------------------|--|

Statistical analysis description:

These analysis are not confirmatory.

|   |   |
|---|---|
| Comparison groups                       | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis | 254   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[77]</sup>   |
| P-value                                 | = 0.7144  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | -0.74   |
| Confidence interval                     |   |
| level                                   | Other: 97.5 %   |
| sides                                   | 2-sided   |
| lower limit                             | -5.25   |
| upper limit                             | 3.78  |

Notes:

[77] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

**Other pre-specified: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 100 - LOCF**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 100 - LOCF |
|-----------------|---|

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 that are all scored from 0-100. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs.

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

End point timeframe:  
Baseline up to Week 100

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 128 <sup>[78]</sup>                    | 134 <sup>[79]</sup>                    | 120 <sup>[80]</sup>                      |  |
| Units: scores on a scale             |  |  |  |  |
| arithmetic mean (standard deviation) | 4.6 (± 17.62)                          | 4.9 (± 20.25)                          | 2.2 (± 16.68)                            |  |

Notes:

[78] - FAS with assessment for this end-point.

[79] - FAS with assessment for this end-point.

[80] - FAS with assessment for this end-point.

## Statistical analyses

| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 248   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[81]</sup>   |
| P-value   | = 0.1792  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | 2.57  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | -1.73   |
| upper limit   | 6.86  |

Notes:

[81] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

| Statistical analysis title  | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 254   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[82]</sup>   |
| P-value   | = 0.5325  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | -1.3  |

|                     |               |
|---------------------|---------------|
| Confidence interval |               |
| level               | Other: 97.5 % |
| sides               | 2-sided       |
| lower limit         | -6            |
| upper limit         | 3.39          |

Notes:

[82] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### Other pre-specified: Change from Baseline in BCVA (Best Corrected Visual Acuity) as Measured by ETDRS Letter Score at Week 148 - LOCF

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in BCVA (Best Corrected Visual Acuity) as Measured by ETDRS Letter Score at Week 148 - LOCF |
|-----------------|--|

End point description:

Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. During year 3 laser subjects received IAI as needed (PRN).

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

End point timeframe:

Baseline up to Week 148

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 136 <sup>[83]</sup>                    | 135 <sup>[84]</sup>                    | 132 <sup>[85]</sup>                      |  |
| Units: letters correctly read        |  |  |  |  |
| arithmetic mean (standard deviation) | 10.3 (± 12.5)                          | 11.7 (± 10.1)                          | 1.6 (± 12.7)                             |  |

Notes:

[83] - FAS

[84] - FAS

[85] - FAS

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Intravitreal Aflibercept Injection 2Q4 vs. Control |
|----------------------------|--|

Statistical analysis description:

These analysis are not confirmatory.

|   |   |
|---|---|
| Comparison groups                       | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis | 268   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[86]</sup>   |
| P-value                                 | < 0.0001  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | 8.7   |
| Confidence interval                     |   |
| level                                   | Other: 97.5 %   |
| sides                                   | 2-sided   |
| lower limit                             | 5.2   |
| upper limit                             | 12.1  |

Notes:

[86] - Stratifying by geographic region (Japan vs non-Japan). LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[87]</sup>   |
| P-value   | < 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | 9.7   |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 6.5   |
| upper limit   | 12.9  |

Notes:

[87] - Stratifying by geographic region (Japan vs non-Japan). LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

#### **Other pre-specified: Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 148 - LOCF**

|  |   |
|--|---|
| End point title  | Percentage of Subjects Who Gained At Least 10 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 148 - LOCF |
| End point description:<br>Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. During year 3 laser subjects received IAI as needed (PRN). |   |
| End point type   | Other pre-specified   |
| End point timeframe:<br>Baseline up to Week 148  |   |

| <b>End point values</b>       | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 136 <sup>[88]</sup>                    | 135 <sup>[89]</sup>                    | 132 <sup>[90]</sup>                      |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 55.9                                   | 56.3                                   | 29.5                                     |  |

Notes:

[88] - FAS

[89] - FAS

[90] - FAS

#### **Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 268   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[91]</sup>   |
| P-value   | < 0.0001  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 26.3  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 13.2  |
| upper limit   | 39.5  |

Notes:

[91] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[92]</sup>   |
| P-value   | < 0.0001  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 26.7  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 13.6  |
| upper limit   | 39.9  |

Notes:

[92] - Stratifying by geographic region (Japan vs non-Japan). The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### **Other pre-specified: Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 148 - LOCF**

|  |   |
|--|---|
| End point title  | Percentage of Subjects Who Gained At Least 15 Letters in BCVA as Measured by ETDRS Letter Score Compared With Baseline at Week 148 - LOCF |
| End point description:<br>Visual function of the study eye was assessed using the ETDRS protocol. A higher score represents better functioning. During year 3 laser subjects received IAI as needed (PRN). |   |
| End point type   | Other pre-specified   |
| End point timeframe:<br>Baseline up to Week 148  |   |

| <b>End point values</b>       | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 136 <sup>[93]</sup>                    | 135 <sup>[94]</sup>                    | 132 <sup>[95]</sup>                      |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 41.2                                   | 42.2                                   | 18.9                                     |  |

Notes:

[93] - FAS

[94] - FAS

[95] - FAS

## Statistical analyses

| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 268   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[96]</sup>   |
| P-value   | < 0.0001  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 22.2  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | 10.1  |
| upper limit   | 34.4  |

Notes:

[96] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
|---|---|
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[97]</sup>   |
| P-value   | < 0.0001  |
| Method  | Cochran-Mantel-Haenszel   |
| Parameter estimate  | CMH adjusted difference   |
| Point estimate  | 23.2  |

|                     |               |
|---------------------|---------------|
| Confidence interval |               |
| level               | Other: 97.5 % |
| sides               | 2-sided       |
| lower limit         | 11            |
| upper limit         | 35.5          |

Notes:

[97] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### Other pre-specified: Percentage of Subjects with a $\geq 2$ -Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 148 - LOCF

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects with a $\geq 2$ -Step Improvement From Baseline in the ETDRS DRSS (Diabetic Retinopathy Severity Score) as Assessed by FP (Fundus Photography) at Week 148 - LOCF |
|-----------------|--|

End point description:

Baseline ETDRS DRSS: None (level 10); Mild to moderate nonproliferative DR (levels 14, 15, 20, 35, and 43); Moderately severe/severe nonproliferative DR (levels 47 and 53); Mild/moderate/high-risk/advanced proliferative DR (levels 61, 65, 71, 75, 81, and 85). During year 3 laser subjects received IAI as needed (PRN).

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

End point timeframe:

Baseline up to Week 148

| End point values              | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed   | 136 <sup>[98]</sup>                    | 135 <sup>[99]</sup>                    | 132 <sup>[100]</sup>                     |  |
| Units: percentage of subjects |  |  |  |  |
| number (not applicable)       | 44.3                                   | 47.8                                   | 17.4                                     |  |

Notes:

[98] - FAS

[99] - FAS

[100] - FAS

### Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:       |   |
| These analysis are not confirmatory.    |   |
| Comparison groups                       | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis | 268   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[101]</sup>  |
| P-value                                 | < 0.0001  |
| Method                                  | Cochran-Mantel-Haenszel   |
| Parameter estimate                      | CMH adjusted difference   |
| Point estimate                          | 26.8  |

|                     |               |
|---------------------|---------------|
| Confidence interval |               |
| level               | Other: 97.5 % |
| sides               | 2-sided       |
| lower limit         | 11.7          |
| upper limit         | 41.9          |

Notes:

[101] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Intravitreal Aflibercept Injection 2Q8 vs. Control |
|-----------------------------------|--|

Statistical analysis description:

These analysis are not confirmatory.

|   |   |
|---|---|
| Comparison groups                       | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis | 267   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[102]</sup>  |
| P-value                                 | < 0.0001  |
| Method                                  | Cochran-Mantel-Haenszel   |
| Parameter estimate                      | CMH adjusted difference   |
| Point estimate                          | 30.2  |

Confidence interval

|             |               |
|-------------|---------------|
| level       | Other: 97.5 % |
| sides       | 2-sided       |
| lower limit | 15.4          |
| upper limit | 45.1          |

Notes:

[102] - Stratifying by geographic region (Japan vs non-Japan).The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### **Other pre-specified: Change from Baseline in Central Retinal Thickness (CRT) at Week 148 as Assessed On Optical Coherence Tomography (OCT) - LOCF**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Central Retinal Thickness (CRT) at Week 148 as Assessed On Optical Coherence Tomography (OCT) - LOCF |
|-----------------|--|

End point description:

During year 3 laser subjects received IAI as needed (PRN).

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

End point timeframe:

Baseline up to Week 148

| <b>End point values</b>              | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 136 <sup>[103]</sup>                   | 135 <sup>[104]</sup>                   | 132 <sup>[105]</sup>                     |  |
| Units: micrometer                    |  |  |  |  |
| arithmetic mean (standard deviation) | -215.2 (± 154.2)                       | -202.8 (± 155)                         | -122.6 (± 176.2)                         |  |



Notes:

[103] - FAS

[104] - FAS

[105] - FAS

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 268   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[106]</sup>  |
| P-value   | < 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | -124.3  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | -160.6  |
| upper limit   | -88   |

Notes:

[106] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 267   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[107]</sup>  |
| P-value   | < 0.0001  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | -98.3   |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | -139.4  |
| upper limit   | -57.1   |

Notes:

[107] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A negative value indicates a result in favor of EYLEA.

## Other pre-specified: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 148 - LOCF

|   |   |
|---|---|
| End point title   | Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Near Activities Subscale at Week 148 - LOCF |
| End point description:<br>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 that are all scored from 0-100. Near activities are defined as reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf. During year 3 laser subjects received IAI as needed (PRN). |   |
| End point type  | Other pre-specified   |
| End point timeframe:<br>Baseline up to Week 14  |   |

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 128 <sup>[108]</sup>                   | 134 <sup>[109]</sup>                   | 120 <sup>[110]</sup>                     |  |
| Units: scores on a scale             |  |  |  |  |
| arithmetic mean (standard deviation) | 8.6 (± 20.86)                          | 9.3 (± 19.94)                          | 5.3 (± 17.34)                            |  |

Notes:

[108] - FAS with assessment for this end point.

[109] - FAS with assessment for this end point.

[110] - FAS with assessment for this end point.

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q4 vs. Control                                |
| Statistical analysis description:<br>These analysis are not confirmatory. |   |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis                                   | 248   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[111]</sup>  |
| P-value   | = 0.0862  |
| Method  | ANCOVA  |
| Parameter estimate  | Mean difference (final values)  |
| Point estimate  | 3.56  |
| Confidence interval   |   |
| level   | Other: 97.5 %   |
| sides   | 2-sided   |
| lower limit   | -1.1  |
| upper limit   | 8.22  |

Notes:

[111] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Intravitreal Aflibercept Injection 2Q8 vs. Control     |
| Statistical analysis description:<br>These analysis are not confirmatory. |  |
| Comparison groups   | Intravitreal Aflibercept Injection 2Q8 v Macular Laser |

|   |                                |
|---|--------------------------------|
|   | Photocoagulation (Control)     |
| Number of subjects included in analysis | 254                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other <sup>[112]</sup>         |
| P-value                                 | = 0.7361                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.72                           |
| Confidence interval                     |                                |
| level                                   | Other: 97.5 %                  |
| sides                                   | 2-sided                        |
| lower limit                             | -4.08                          |
| upper limit                             | 5.52                           |

Notes:

[112] - Treatment group and geographic region (Japan vs. Non-Japan) as factors and baseline value as covariate. LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

### Other pre-specified: Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 148 - LOCF

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in National Eye Institute 25-Item Visual Function Questionnaire (NEI VFQ-25) Distance Activities Subscale at Week 148 - LOCF |
|-----------------|---|

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 that are all scored from 0-100. Distance activities are defined as reading street signs or names on stores, and going down stairs, steps, or curbs. During year 3 laser subjects received IAI as needed (PRN).

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

End point timeframe:

Baseline up to Week 148

| End point values                     | Intravitreal Aflibercept Injection 2Q4 | Intravitreal Aflibercept Injection 2Q8 | Macular Laser Photocoagulation (Control) |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group                        | Reporting group                          |  |
| Number of subjects analysed          | 128 <sup>[113]</sup>                   | 134 <sup>[114]</sup>                   | 120 <sup>[115]</sup>                     |  |
| Units: score on a scale              |  |  |  |  |
| arithmetic mean (standard deviation) | 4.4 (± 17.61)                          | 7.4 (± 21.66)                          | 3.4 (± 17.19)                            |  |

Notes:

[113] - FAS with assessment for this end-point.

[114] - FAS with assessment for this end-point.

[115] - FAS with assessment for this end-point.

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Intravitreal Aflibercept Injection 2Q4 vs. Control |
|----------------------------|--|

Statistical analysis description:

These analysis are not confirmatory.

|                   |   |
|-------------------|---|
| Comparison groups | Intravitreal Aflibercept Injection 2Q4 v Macular Laser Photocoagulation (Control) |
|-------------------|---|

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 248                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other <sup>[116]</sup>         |
| P-value                                 | = 0.5337                       |
| Method                                  | ANCOVA                         |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1.16                           |
| Confidence interval                     |                                |
| level                                   | Other: 97.5 %                  |
| sides                                   | 2-sided                        |
| lower limit                             | -3.02                          |
| upper limit                             | 5.34                           |

Notes:

[116] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | Intravitreal Aflibercept Injection 2Q8 vs. Control                                |
| Statistical analysis description:       |   |
| These analysis are not confirmatory.    |   |
| Comparison groups                       | Intravitreal Aflibercept Injection 2Q8 v Macular Laser Photocoagulation (Control) |
| Number of subjects included in analysis | 254   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | other <sup>[117]</sup>  |
| P-value                                 | = 0.8323  |
| Method                                  | ANCOVA  |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | -0.46   |
| Confidence interval                     |   |
| level                                   | Other: 97.5 %   |
| sides                                   | 2-sided   |
| lower limit                             | -5.34   |
| upper limit                             | 4.42  |

Notes:

[117] - LS mean difference from ANCOVA. The estimate is calculated as EYLEA minus Laser. A positive value indicates a result in favor of EYLEA.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

For each subject from his first study drug injection until 30 days after the last study drug injection at the latest up to termination visit at Week 148

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Intravitreal Aflibercept Injection 2Q4 |
|-----------------------|--|

Reporting group description:

Participants received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks (2Q4).

|                       |  |
|-----------------------|--|
| Reporting group title | Macular Laser Photocoagulation (Control) |
|-----------------------|--|

Reporting group description:

Participants received laser treatment at baseline and as needed at visits at which laser retreatment criteria were met, but no more frequently than every 12 weeks. During year 3 laser patients could receive IAI as needed (PRN) .

|                       |  |
|-----------------------|--|
| Reporting group title | Intravitreal Aflibercept Injection 2Q8 |
|-----------------------|--|

Reporting group description:

Participants received 2mg Intravitreal aflibercept injection (IAI) (EYLEA, VEGF Trap-Eye, BAY86-5321) every 4 weeks for 5 visits followed by injections every 8 weeks (2Q8).

| Serious adverse events  | Intravitreal Aflibercept Injection 2Q4 | Macular Laser Photocoagulation (Control) | Intravitreal Aflibercept Injection 2Q8 |
|---|--|--|--|
| Total subjects affected by serious adverse events                   |  |  |  |
| subjects affected / exposed   | 63 / 136 (46.32%)                      | 51 / 133 (38.35%)                        | 60 / 135 (44.44%)                      |
| number of deaths (all causes)                                       | 7                                      | 3  | 7                                      |
| number of deaths resulting from adverse events                      |  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Adenocarcinoma of colon   |  |  |  |
| subjects affected / exposed   | 0 / 136 (0.00%)                        | 0 / 133 (0.00%)                          | 1 / 135 (0.74%)                        |
| occurrences causally related to treatment / all                     | 0 / 0                                  | 0 / 0                                    | 0 / 1                                  |
| deaths causally related to treatment / all                          | 0 / 0                                  | 0 / 0                                    | 0 / 0                                  |
| Adrenal neoplasm  |  |  |  |
| subjects affected / exposed   | 1 / 136 (0.74%)                        | 0 / 133 (0.00%)                          | 0 / 135 (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                                  |
| Anaplastic astrocytoma  |  |  |  |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| B-cell lymphoma                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Bladder neoplasm                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Breast cancer                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Colon cancer                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Lung neoplasm                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastases to liver                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastases to lung                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Neoplasm malignant                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Pancreatic carcinoma stage IV                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer stage I                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Prostate cancer stage III                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal neoplasm                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 136 (1.47%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Uterine leiomyoma                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Vascular disorders                              |                 |                 |                 |
| Arterial haemorrhage                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriosclerosis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Circulatory collapse                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Deep vein thrombosis                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lymphoedema                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Peripheral arterial occlusive disease           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 3 / 133 (2.26%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery stenosis                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Peripheral ischaemia                            |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Surgical and medical procedures                 |                 |                 |                 |
| Arteriovenous shunt operation                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Cataract operation                              |                 |                 |                 |
| subjects affected / exposed                     | 3 / 136 (2.21%) | 2 / 133 (1.50%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip arthroplasty                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteosynthesis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Peripheral artery bypass                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Radical prostatectomy                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Transurethral prostatectomy                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Vitreotomy                                      |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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 |                 |                 |                 |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Death  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Device failure                                       |                 |                 |                 |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Generalised oedema                                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Injection site injury                                |                 |                 |                 |
| subjects affected / exposed                          | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Oedema peripheral                                    |                 |                 |                 |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders             |                 |                 |                 |
| Benign prostatic hyperplasia                         |                 |                 |                 |
| subjects affected / exposed                          | 0 / 136 (0.00%) | 2 / 133 (1.50%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Uterine polyp                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Uterine prolapse                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Hydrothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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 failure                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Sleep apnoea syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Suicide attempt                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Investigations                                  |                 |                 |                 |
| Catheterisation cardiac                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Electrocardiogram ST segment depression         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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 tests abnormal                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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  |                 |                 |                 |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain contusion                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain herniation                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Fracture  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Head injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Humerus fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 3 / 136 (2.21%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Lower limb fracture                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Meniscus injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thermal burn                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Tibia fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Traumatic arthrosis                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Traumatic fracture                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 136 (1.47%) | 3 / 133 (2.26%) | 0 / 135 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 1           | 0 / 0           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arrhythmia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Atrioventricular block complete                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bundle branch block right                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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 disorder                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 136 (0.74%) | 2 / 133 (1.50%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Cardiac failure acute                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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 failure chronic                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac sarcoidosis                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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 valve disease                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiogenic shock                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 136 (1.47%) | 1 / 133 (0.75%) | 0 / 135 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery stenosis                        |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 136 (1.47%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Hypertensive heart disease                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 1 / 1           |
| Ischaemic cardiomyopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Left ventricular failure                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Mitral valve stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 4 / 136 (2.94%) | 1 / 133 (0.75%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 1 / 2           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Ventricular arrhythmia                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Ventricular tachycardia                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Nervous system disorders                        |                 |                 |                 |
| Brain stem infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Cauda equina syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Cerebral atrophy                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Cerebral haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 4 / 136 (2.94%) | 1 / 133 (0.75%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 136 (1.47%) | 1 / 133 (0.75%) | 0 / 135 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Loss of consciousness                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Nerve compression</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| <b>Peripheral sensorimotor neuropathy</b>       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| <b>Syncope</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |                 |
| <b>Anaemia</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Immune thrombocytopenic purpura</b>          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| <b>Neutropenia</b>                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Ear and labyrinth disorders</b>              |                 |                 |                 |
| <b>Deafness</b>                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| <b>Vertigo</b>                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| 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                     | 5 / 136 (3.68%) | 2 / 133 (1.50%) | 7 / 135 (5.19%) |
| occurrences causally related to treatment / all | 1 / 8           | 0 / 2           | 2 / 11          |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cataract subcapsular                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic retinopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 133 (1.50%) | 0 / 135 (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           |
| Iridocyclitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Macular degeneration                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Macular fibrosis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Macular hole                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Optic atrophy                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Posterior capsule opacification                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Retinal artery occlusion                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Retinal detachment                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal exudates                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Retinal neovascularisation                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 3 / 133 (2.26%) | 0 / 135 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal vascular disorder                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Retinopathy proliferative                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Vitreous haemorrhage                            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 4 / 136 (2.94%) | 2 / 133 (1.50%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 4           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain upper                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           | 0 / 0           |
| Enterocolitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Gastric ulcer                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ileus   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Rectal haemorrhage                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Reflux gastritis                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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                         |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic cirrhosis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Dermal cyst                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Diabetic foot                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 2 / 133 (1.50%) | 0 / 135 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psoriasis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 133 (1.50%) | 0 / 135 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin ulcer                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 133 (1.50%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic kidney disease                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Renal artery stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal impairment                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Stress urinary incontinence                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Endocrine disorders                             |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Toxic nodular goitre                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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 |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Arthropathy                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Lumbar spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 133 (1.50%) | 0 / 135 (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           |
| Metatarsalgia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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 disorder                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Neck pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 136 (1.47%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Polymyalgia rheumatica                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rotator cuff syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal column stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal pain                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Spondylolisthesis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Synovitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Tenosynovitis stenosans                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 133 (1.50%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis infective                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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 / 136 (0.74%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Gangrene  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infected dermal cyst                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Infected skin ulcer                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Osteomyelitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Pilonidal cyst                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 3 / 135 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Salmonellosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Diabetes mellitus                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 1 / 133 (0.75%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic ketoacidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fluid retention                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 2 / 133 (1.50%) | 2 / 135 (1.48%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 1 / 133 (0.75%) | 0 / 135 (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           |
| Ketoacidosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 136 (0.00%) | 0 / 133 (0.00%) | 1 / 135 (0.74%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Type 2 diabetes mellitus                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 136 (0.74%) | 0 / 133 (0.00%) | 0 / 135 (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           |

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

| <b>Non-serious adverse events</b>                     | Intravitreal<br>Aflibercept Injection<br>2Q4 | Macular Laser<br>Photocoagulation<br>(Control) | Intravitreal<br>Aflibercept Injection<br>2Q8 |
|---|--|--|--|
| Total subjects affected by non-serious adverse events |  |  |  |
| subjects affected / exposed                           | 117 / 136 (86.03%)                           | 113 / 133 (84.96%)                             | 122 / 135 (90.37%)                           |
| Investigations  |  |  |  |
| Blood creatinine increased                            |  |  |  |
| subjects affected / exposed                           | 7 / 136 (5.15%)                              | 5 / 133 (3.76%)                                | 6 / 135 (4.44%)                              |
| occurrences (all)                                     | 8  | 5  | 6  |
| Blood glucose increased                               |  |  |  |
| subjects affected / exposed                           | 10 / 136 (7.35%)                             | 8 / 133 (6.02%)                                | 7 / 135 (5.19%)                              |
| occurrences (all)                                     | 13   | 10   | 8  |
| Blood urea increased                                  |  |  |  |

|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 6 / 136 (4.41%)<br>8    | 6 / 133 (4.51%)<br>7    | 10 / 135 (7.41%)<br>10  |
| Glycosylated haemoglobin increased<br>subjects affected / exposed<br>occurrences (all)              | 12 / 136 (8.82%)<br>15  | 11 / 133 (8.27%)<br>11  | 11 / 135 (8.15%)<br>12  |
| Intraocular pressure increased<br>subjects affected / exposed<br>occurrences (all)                  | 28 / 136 (20.59%)<br>77 | 16 / 133 (12.03%)<br>32 | 18 / 135 (13.33%)<br>51 |
| Visual acuity tests abnormal<br>subjects affected / exposed<br>occurrences (all)                    | 19 / 136 (13.97%)<br>35 | 32 / 133 (24.06%)<br>49 | 22 / 135 (16.30%)<br>63 |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)              | 23 / 136 (16.91%)<br>32 | 24 / 133 (18.05%)<br>41 | 25 / 135 (18.52%)<br>37 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 6 / 136 (4.41%)<br>6    | 8 / 133 (6.02%)<br>8    | 3 / 135 (2.22%)<br>3    |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)                       | 31 / 136 (22.79%)<br>43 | 17 / 133 (12.78%)<br>29 | 26 / 135 (19.26%)<br>37 |
| Cataract cortical<br>subjects affected / exposed<br>occurrences (all)                               | 7 / 136 (5.15%)<br>12   | 1 / 133 (0.75%)<br>3    | 6 / 135 (4.44%)<br>7    |
| Conjunctival haemorrhage<br>subjects affected / exposed<br>occurrences (all)                        | 43 / 136 (31.62%)<br>59 | 17 / 133 (12.78%)<br>26 | 39 / 135 (28.89%)<br>58 |
| Cataract subcapsular<br>subjects affected / exposed<br>occurrences (all)                            | 11 / 136 (8.09%)<br>16  | 4 / 133 (3.01%)<br>4    | 5 / 135 (3.70%)<br>6    |
| Conjunctival hyperaemia<br>subjects affected / exposed<br>occurrences (all)                         | 8 / 136 (5.88%)<br>10   | 9 / 133 (6.77%)<br>15   | 3 / 135 (2.22%)<br>5    |
| Corneal erosion   |                         |                         |                         |

|                                 |                   |                   |                   |
|---------------------------------|-------------------|-------------------|-------------------|
| subjects affected / exposed     | 9 / 136 (6.62%)   | 7 / 133 (5.26%)   | 8 / 135 (5.93%)   |
| occurrences (all)               | 11                | 16                | 10                |
| Cystoid macular oedema          |                   |                   |                   |
| subjects affected / exposed     | 10 / 136 (7.35%)  | 18 / 133 (13.53%) | 20 / 135 (14.81%) |
| occurrences (all)               | 18                | 51                | 67                |
| Diabetic retinal oedema         |                   |                   |                   |
| subjects affected / exposed     | 33 / 136 (24.26%) | 18 / 133 (13.53%) | 23 / 135 (17.04%) |
| occurrences (all)               | 49                | 25                | 44                |
| Dry eye                         |                   |                   |                   |
| subjects affected / exposed     | 5 / 136 (3.68%)   | 8 / 133 (6.02%)   | 5 / 135 (3.70%)   |
| occurrences (all)               | 9                 | 13                | 7                 |
| Eye pain                        |                   |                   |                   |
| subjects affected / exposed     | 15 / 136 (11.03%) | 10 / 133 (7.52%)  | 10 / 135 (7.41%)  |
| occurrences (all)               | 34                | 15                | 19                |
| Macular fibrosis                |                   |                   |                   |
| subjects affected / exposed     | 10 / 136 (7.35%)  | 11 / 133 (8.27%)  | 12 / 135 (8.89%)  |
| occurrences (all)               | 13                | 14                | 17                |
| Macular oedema                  |                   |                   |                   |
| subjects affected / exposed     | 21 / 136 (15.44%) | 22 / 133 (16.54%) | 20 / 135 (14.81%) |
| occurrences (all)               | 41                | 46                | 31                |
| Ocular hyperaemia               |                   |                   |                   |
| subjects affected / exposed     | 5 / 136 (3.68%)   | 4 / 133 (3.01%)   | 7 / 135 (5.19%)   |
| occurrences (all)               | 12                | 5                 | 9                 |
| Ocular hypertension             |                   |                   |                   |
| subjects affected / exposed     | 10 / 136 (7.35%)  | 6 / 133 (4.51%)   | 4 / 135 (2.96%)   |
| occurrences (all)               | 21                | 7                 | 9                 |
| Posterior capsule opacification |                   |                   |                   |
| subjects affected / exposed     | 10 / 136 (7.35%)  | 10 / 133 (7.52%)  | 12 / 135 (8.89%)  |
| occurrences (all)               | 15                | 18                | 15                |
| Punctate keratitis              |                   |                   |                   |
| subjects affected / exposed     | 7 / 136 (5.15%)   | 8 / 133 (6.02%)   | 11 / 135 (8.15%)  |
| occurrences (all)               | 13                | 14                | 19                |
| Retinal aneurysm                |                   |                   |                   |
| subjects affected / exposed     | 14 / 136 (10.29%) | 9 / 133 (6.77%)   | 12 / 135 (8.89%)  |
| occurrences (all)               | 26                | 16                | 26                |
| Retinal exudates                |                   |                   |                   |

|  |                         |                         |                         |
|--|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)   | 20 / 136 (14.71%)<br>38 | 15 / 133 (11.28%)<br>32 | 22 / 135 (16.30%)<br>49 |
| Retinal haemorrhage<br>subjects affected / exposed<br>occurrences (all)  | 21 / 136 (15.44%)<br>35 | 21 / 133 (15.79%)<br>63 | 25 / 135 (18.52%)<br>64 |
| Retinal vascular disorder<br>subjects affected / exposed<br>occurrences (all)                                    | 9 / 136 (6.62%)<br>20   | 5 / 133 (3.76%)<br>10   | 8 / 135 (5.93%)<br>13   |
| Vitreous detachment<br>subjects affected / exposed<br>occurrences (all)  | 9 / 136 (6.62%)<br>12   | 5 / 133 (3.76%)<br>7    | 10 / 135 (7.41%)<br>11  |
| Visual acuity reduced<br>subjects affected / exposed<br>occurrences (all)  | 33 / 136 (24.26%)<br>64 | 30 / 133 (22.56%)<br>57 | 33 / 135 (24.44%)<br>81 |
| Vitreous floaters<br>subjects affected / exposed<br>occurrences (all)  | 13 / 136 (9.56%)<br>14  | 4 / 133 (3.01%)<br>4    | 5 / 135 (3.70%)<br>7    |
| Vitreous haemorrhage<br>subjects affected / exposed<br>occurrences (all)   | 7 / 136 (5.15%)<br>14   | 8 / 133 (6.02%)<br>12   | 11 / 135 (8.15%)<br>11  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)     | 7 / 136 (5.15%)<br>10   | 7 / 133 (5.26%)<br>10   | 6 / 135 (4.44%)<br>6    |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 4 / 136 (2.94%)<br>5    | 11 / 133 (8.27%)<br>11  | 3 / 135 (2.22%)<br>3    |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 136 (0.74%)<br>1    | 1 / 133 (0.75%)<br>1    | 9 / 135 (6.67%)<br>9    |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                    | 12 / 136 (8.82%)<br>16  | 9 / 133 (6.77%)<br>10   | 5 / 135 (3.70%)<br>5    |
| Conjunctivitis   |                         |                         |                         |



|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)  | 14 / 136 (10.29%)<br>16 | 8 / 133 (6.02%)<br>10   | 13 / 135 (9.63%)<br>20  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)   | 7 / 136 (5.15%)<br>10   | 13 / 133 (9.77%)<br>16  | 11 / 135 (8.15%)<br>11  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)   | 38 / 136 (27.94%)<br>67 | 34 / 133 (25.56%)<br>62 | 39 / 135 (28.89%)<br>69 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                 | 6 / 136 (4.41%)<br>8    | 6 / 133 (4.51%)<br>11   | 11 / 135 (8.15%)<br>22  |
| Metabolism and nutrition disorders<br>Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all) | 6 / 136 (4.41%)<br>6    | 9 / 133 (6.77%)<br>10   | 10 / 135 (7.41%)<br>12  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 15 February 2011 | - The guidelines for additional treatment of inadequate responders were revised. - Alternative statistical analysis plans were allowed for the data results according to the regulatory requirements of the governing Health Authority. - The number of initial monthly doses for subjects in the 2Q8 group was changed to 5 (total). |
| 28 May 2013      | - The treatment of the fellow eye (non-study eye) was clarified. - The secondary efficacy endpoints were revised. - The statistical methodology section was modified to be consistent with the revisions in the SAP.  |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25012934>

<http://www.ncbi.nlm.nih.gov/pubmed/26198808>

<http://www.ncbi.nlm.nih.gov/pubmed/26056030>