



## Clinical trial results:

### A Two-Year, Two-Arm, Randomized, Double Masked, Multicenter, Phase III Study Assessing the Efficacy and Safety of Brolucizumab versus Aflibercept in Adult Patients with Visual Impairment due to Diabetic Macular Edema

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2017-003960-11                   |
| Trial protocol           | DE LV LT SK SE BE DK HU CZ BG PL |
| Global end of trial date | 08 June 2021                     |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 17 June 2022 |
| First version publication date | 17 June 2022 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRTH258B2302 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03481660 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |              |
|------------------------------------------------------|--------------|
| Analysis stage                                       | Final        |
| Date of interim/final analysis                       | 08 June 2021 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 08 June 2021 |
| Was the trial ended prematurely?                     | No           |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that brolocizumab was non-inferior to aflibercept with respect to the visual outcome after the first year of treatment

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 27 July 2018 |
| 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 | Belgium: 3             |
| Country: Number of subjects enrolled | Bulgaria: 8            |
| Country: Number of subjects enrolled | Czechia: 22            |
| Country: Number of subjects enrolled | Denmark: 3             |
| Country: Number of subjects enrolled | Estonia: 3             |
| Country: Number of subjects enrolled | France: 56             |
| Country: Number of subjects enrolled | Germany: 17            |
| Country: Number of subjects enrolled | Hungary: 47            |
| Country: Number of subjects enrolled | India: 24              |
| Country: Number of subjects enrolled | Korea, Republic of: 19 |
| Country: Number of subjects enrolled | Latvia: 4              |
| Country: Number of subjects enrolled | Lebanon: 4             |
| Country: Number of subjects enrolled | Lithuania: 7           |
| Country: Number of subjects enrolled | Malaysia: 15           |
| Country: Number of subjects enrolled | Norway: 4              |
| Country: Number of subjects enrolled | Poland: 13             |
| Country: Number of subjects enrolled | Russian Federation: 17 |
| Country: Number of subjects enrolled | Singapore: 7           |
| Country: Number of subjects enrolled | Slovakia: 32           |

|                                      |                |
|--------------------------------------|----------------|
| Country: Number of subjects enrolled | Sweden: 1      |
| Country: Number of subjects enrolled | Switzerland: 7 |
| Country: Number of subjects enrolled | Taiwan: 24     |
| Country: Number of subjects enrolled | Turkey: 23     |
| Worldwide total number of subjects   | 360            |
| EEA total number of subjects         | 220            |

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)                      | 202 |
| From 65 to 84 years                       | 156 |
| 85 years and over                         | 2   |

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted in 79 centers in 23 countries worldwide.

### Pre-assignment

Screening details:

360 subjects were randomized in a 1:1 ratio to brolucizumab 6 mg arm (n=179) or aflibercept 2 mg arm (n=181).

### Period 1

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

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Brolucizumab 6 mg |
|------------------|-------------------|

Arm description:

Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule

|                                        |                                                                                 |
|----------------------------------------|---------------------------------------------------------------------------------|
| Arm type                               | Experimental                                                                    |
| Investigational medicinal product name | Brolucizumab                                                                    |
| Investigational medicinal product code |                                                                                 |
| Other name                             | RTH258, ESBA1008                                                                |
| Pharmaceutical forms                   | Injection, Solution for injection, Solution for injection in pre-filled syringe |
| Routes of administration               | Intravitreal use                                                                |

Dosage and administration details:

Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Aflibercept 2 mg |
|------------------|------------------|

Arm description:

Aflibercept 2 mg/0.05 mL, as labeled, 5 loading doses, with subsequent doses every 8 weeks

|                                        |                                                                                 |
|----------------------------------------|---------------------------------------------------------------------------------|
| Arm type                               | Active comparator                                                               |
| Investigational medicinal product name | Aflibercept                                                                     |
| Investigational medicinal product code |                                                                                 |
| Other name                             | Eylea                                                                           |
| Pharmaceutical forms                   | Injection, Solution for injection, Solution for injection in pre-filled syringe |
| Routes of administration               | Intravitreal use                                                                |

Dosage and administration details:

Aflibercept 2 mg/0.05 mL, as labeled, 5 loading doses, with subsequent doses every 8 weeks

| <b>Number of subjects in period 1</b> | Brolucizumab 6 mg | Aflibercept 2 mg |
|---------------------------------------|-------------------|------------------|
| Started                               | 179               | 181              |
| Completed                             | 143               | 156              |
| Not completed                         | 36                | 25               |
| Adverse event, serious fatal          | 13                | 9                |
| Consent withdrawn by subject          | 14                | 7                |
| Physician decision                    | 2                 | 3                |
| Adverse event, non-fatal              | 5                 | 4                |
| Lost to follow-up                     | 2                 | 2                |

## Baseline characteristics

### Reporting groups

|                                                                                                                                               |                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Reporting group title                                                                                                                         | Brolucizumab 6 mg |
| Reporting group description:<br>Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule |                   |
| Reporting group title                                                                                                                         | Aflibercept 2 mg  |
| Reporting group description:<br>Aflibercept 2 mg/0.05 mL, as labeled, 5 loading doses, with subsequent doses every 8 weeks                    |                   |

| Reporting group values                    | Brolucizumab 6 mg | Aflibercept 2 mg | Total |
|-------------------------------------------|-------------------|------------------|-------|
| Number of subjects                        | 179               | 181              | 360   |
| Age Categorical<br>Units: Participants    |                   |                  |       |
| < 65 years                                | 100               | 102              | 202   |
| >= 65 years                               | 79                | 79               | 158   |
| Age Continuous<br>Units: Years            |                   |                  |       |
| arithmetic mean                           | 62.3              | 62.2             | -     |
| standard deviation                        | ± 10.55           | ± 9.48           | -     |
| Sex: Female, Male<br>Units: Participants  |                   |                  |       |
| Female                                    | 59                | 66               | 125   |
| Male                                      | 120               | 115              | 235   |
| Race (NIH/OMB)<br>Units: Subjects         |                   |                  |       |
| American Indian or Alaska Native          | 0                 | 0                | 0     |
| Asian                                     | 43                | 48               | 91    |
| Native Hawaiian or Other Pacific Islander | 0                 | 0                | 0     |
| Black or African American                 | 3                 | 1                | 4     |
| White                                     | 133               | 132              | 265   |
| More than one race                        | 0                 | 0                | 0     |
| Unknown or Not Reported                   | 0                 | 0                | 0     |
| Ethnicity (NIH/OMB)<br>Units: Subjects    |                   |                  |       |
| Hispanic or Latino                        | 3                 | 4                | 7     |
| Not Hispanic or Latino                    | 163               | 170              | 333   |
| Unknown or Not Reported                   | 13                | 7                | 20    |

## End points

### End points reporting groups

|                                                                                                                                               |                   |
|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Reporting group title                                                                                                                         | Brolucizumab 6 mg |
| Reporting group description:<br>Brolucizumab 6 mg/0.05 mL, 5 loading doses, with subsequent doses per protocol-specified maintenance schedule |                   |
| Reporting group title                                                                                                                         | Aflibercept 2 mg  |
| Reporting group description:<br>Aflibercept 2 mg/0.05 mL, as labeled, 5 loading doses, with subsequent doses every 8 weeks                    |                   |

### Primary: Mean change from Baseline in best-corrected visual acuity (BCVA) at Week 52 for the study eye

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Mean change from Baseline in best-corrected visual acuity (BCVA) at Week 52 for the study eye |
| End point description:<br>Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment. |                                                                                               |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Primary                                                                                       |
| End point timeframe:<br>Baseline, Week 52                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                               |

| End point values                             | Brolucizumab 6 mg  | Aflibercept 2 mg  |  |  |
|----------------------------------------------|--------------------|-------------------|--|--|
| Subject group type                           | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed                  | 179                | 181               |  |  |
| Units: Scores on a scale                     |                    |                   |  |  |
| least squares mean (confidence interval 95%) | 10.6 (9.3 to 11.9) | 9.4 (8.1 to 10.7) |  |  |

### Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | BCVA at Week 52                      |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | non-inferiority <sup>[1]</sup>       |
| P-value                                 | < 0.001                              |
| Method                                  | ANOVA                                |
| Parameter estimate                      | LS mean difference                   |
| Point estimate                          | 1.2                                  |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.6                       |
| upper limit          | 3.1                        |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.94                       |

Notes:

[1] - (4-letter margin) (1-sided)

## Secondary: Average mean change from Baseline in BCVA over the period Week 40 through Week 52 for the study eye

|                 |                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------|
| End point title | Average mean change from Baseline in BCVA over the period Week 40 through Week 52 for the study eye |
|-----------------|-----------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. For each participants, this endpoint was defined as the mean change from baseline to the average value over the period Week 40 through Week 52. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, period Week 40 through Week 52

| End point values                             | Brolucizumab 6 mg  | Aflibercept 2 mg  |  |  |
|----------------------------------------------|--------------------|-------------------|--|--|
| Subject group type                           | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed                  | 179                | 181               |  |  |
| Units: Scores on a scale                     |                    |                   |  |  |
| least squares mean (confidence interval 95%) | 10.3 (9.1 to 11.5) | 9.4 (8.2 to 10.6) |  |  |

## Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Statistical analysis title              | BCVA over period Week 40 through Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg     |
| Number of subjects included in analysis | 360                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.164                                  |
| Method                                  | ANOVA                                    |

|  |                                          |
|--|------------------------------------------|
|  | BCVA over period Week 40 through Week 52 |
|--|------------------------------------------|

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       |                                      |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | non-inferiority <sup>[2]</sup>       |
| P-value                                 | < 0.001                              |
| Method                                  | ANOVA                                |
| Parameter estimate                      | LS mean difference                   |
| Point estimate                          | 0.9                                  |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -0.9                                 |
| upper limit                             | 2.6                                  |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 0.88                                 |

Notes:

[2] - (4-letter margin) (1-sided)

### **Secondary: (Brolucizumab treatment arm only): Percentage of participants maintained at q12w up to Week 52 and up to q12w/q16w up to Week 100.**

|                 |                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title | (Brolucizumab treatment arm only): Percentage of participants maintained at q12w up to Week 52 and up to q12w/q16w up to Week 100. |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

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

End point timeframe:

Week 52, Week 100

| <b>End point values</b>           | Brolucizumab 6 mg   | Aflibercept 2 mg |  |  |
|-----------------------------------|---------------------|------------------|--|--|
| Subject group type                | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed       | 179                 | 0 <sup>[3]</sup> |  |  |
| Units: Percentage of participants |                     |                  |  |  |
| number (confidence interval 95%)  |                     |                  |  |  |
| Week 48                           | 50.3 (42.5 to 57.7) | ( to )           |  |  |
| Week 96                           | 36.8 (29.1 to 45.5) | ( to )           |  |  |

Notes:

[3] - Endpoint applicable to Brolucizumab treatment arm only

### **Statistical analyses**

No statistical analyses for this end point

**Secondary: (Brolucizumab treatment arm only): Percentage of participants maintained at q12w up to Week 52 within those patients that qualified for q12w at Week 36**

|                 |                                                                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | (Brolucizumab treatment arm only): Percentage of participants maintained at q12w up to Week 52 within those patients that qualified for q12w at Week 36 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

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

End point timeframe:

Week 36, Week 52

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg |  |  |
|-----------------------------------|---------------------|------------------|--|--|
| Subject group type                | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed       | 87                  | 0 <sup>[4]</sup> |  |  |
| Units: Percentage of participants |                     |                  |  |  |
| number (confidence interval 95%)  | 95.1 (87.4 to 98.1) | ( to )           |  |  |

Notes:

[4] - Endpoint applicable to Brolucizumab treatment arm only

**Statistical analyses**

No statistical analyses for this end point

**Secondary: (Brolucizumab treatment arm only): Percentage of participants maintained at q12w/q16w up to Week 100, within those patients that qualified for q12w at Week 36**

|                 |                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | (Brolucizumab treatment arm only): Percentage of participants maintained at q12w/q16w up to Week 100, within those patients that qualified for q12w at Week 36 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Disease activity assessments (DAAs) were performed to identify q8w-need at pre-specified visits (Weeks 32, 36, 48, 60, 72 and every visit from Week 72 through Week 96). Weeks 32 and 36 were the two DAA visits of the initial q12w cycle after the loading phase of the brolucizumab arm. At Week 72 or Week 76 (if DAA/disease stability assessment was missed at Week 72), participants in the brolucizumab were evaluated for an additional 4-week dose regimen extension.

The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

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

End point timeframe:

Week 36, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg |  |  |
|-----------------------------------|---------------------|------------------|--|--|
| Subject group type                | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed       | 87                  | 0 <sup>[5]</sup> |  |  |
| Units: Percentage of participants |                     |                  |  |  |
| number (confidence interval 95%)  | 69.6 (57.4 to 78.9) | ( to )           |  |  |

Notes:

[5] - Endpoint applicable to Brolucizumab treatment arm only

## Statistical analyses

No statistical analyses for this end point

### Secondary: (Brolucizumab treatment arm only): Percentage of participants maintained on q16w up to Week 100 within the patients on q12w at Week 68 and on q16w at Week 76

|                 |                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | (Brolucizumab treatment arm only): Percentage of participants maintained on q16w up to Week 100 within the patients on q12w at Week 68 and on q16w at Week 76 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Disease activity assessments (DAAs) were performed to identify q8w-need at pre-specified visits (Weeks 32, 36, 48, 60, 72 and every visit from Week 72 through Week 96). Weeks 32 and 36 were the two DAA visits of the initial q12w cycle after the loading phase of the brolucizumab arm. At Week 72 or Week 76 (if DAA/disease stability assessment was missed at Week 72), participants in the brolucizumab were evaluated for an additional 4-week dose regimen extension.

The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

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

End point timeframe:

Week 68, Week 76, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg |  |  |
|-----------------------------------|---------------------|------------------|--|--|
| Subject group type                | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed       | 44                  | 0 <sup>[6]</sup> |  |  |
| Units: Percentage of participants |                     |                  |  |  |
| number (confidence interval 95%)  | 87.9 (73.3 to 94.8) | ( to )           |  |  |

Notes:

[6] - Endpoint applicable to Brolucizumab treatment arm only

## Statistical analyses

No statistical analyses for this end point

### Secondary: (Brolucizumab treatment arm only): Percentage of participants re-assigned and maintained on q12w up to Week 100 within the patients on q8w at Week 68 and on q12w at Week 80

|                 |                                                                                                                        |
|-----------------|------------------------------------------------------------------------------------------------------------------------|
| End point title | (Brolucizumab treatment arm only): Percentage of participants re-assigned and maintained on q12w up to Week 100 within |
|-----------------|------------------------------------------------------------------------------------------------------------------------|

## End point description:

Disease activity assessments (DAAs) were performed to identify q8w-need at pre-specified visits (Weeks 32, 36, 48, 60, 72 and every visit from Week 72 through Week 96). Weeks 32 and 36 were the two DAA visits of the initial q12w cycle after the loading phase of the brolucizumab arm. At Week 72 or Week 76 (if DAA/disease stability assessment was missed at Week 72), participants in the brolucizumab were evaluated for an additional 4-week dose regimen extension.

The number of participants maintaining every 12 weeks (q12w) treatment status in the Brolucizumab arm was derived based on Kaplan-Meier estimates time-to-first q8w treatment need. Positive treatment status was defined as intravitreal treatment (IVT) injections per planned dosing regimen [every 12 weeks (q12w)].

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

## End point timeframe:

|                            |
|----------------------------|
| Week 68, Week 80, Week 100 |
|----------------------------|

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg |  |  |
|-----------------------------------|---------------------|------------------|--|--|
| Subject group type                | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed       | 34                  | 0 <sup>[7]</sup> |  |  |
| Units: Percentage of participants |                     |                  |  |  |
| number (confidence interval 95%)  | 73.1 (54.5 to 85.0) | ( to )           |  |  |

Notes:

[7] - Endpoint applicable to Brolucizumab treatment arm only

## Statistical analyses

|                                            |
|--------------------------------------------|
| No statistical analyses for this end point |
|--------------------------------------------|

**Secondary: (Brolucizumab treatment arm only): Number of participants with injections per planned dosing regimen (every 8, 12 or 16 weeks)**

|                 |                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|
| End point title | (Brolucizumab treatment arm only): Number of participants with injections per planned dosing regimen (every 8, 12 or 16 weeks) |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Reported categorically for the subjects who completed the study treatment period: every 8 weeks (q8w), Every 12 weeks (q12w), Every 16 weeks (q16w)

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

## End point timeframe:

|          |
|----------|
| Week 100 |
|----------|

| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 141               | 0 <sup>[8]</sup> |  |  |
| Units: Participants         |                   |                  |  |  |
| q8w                         | 74                |                  |  |  |
| q12w                        | 32                |                  |  |  |
| q16w                        | 35                |                  |  |  |

Notes:

[8] - Endpoint applicable to Brolucizumab treatment arm only

## Statistical analyses

No statistical analyses for this end point

### Secondary: Mean change from Baseline in Best Corrected Visual Acuity (BCVA) at each visit up to Week 100 for the study eye

|                 |                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline in Best Corrected Visual Acuity (BCVA) at each visit up to Week 100 for the study eye |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The BCVA score is the number of letters read correctly by the patient, hence an increase in score indicates improvement in acuity. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                             | Brolucizumab 6 mg  | Aflibercept 2 mg  |  |  |
|----------------------------------------------|--------------------|-------------------|--|--|
| Subject group type                           | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed                  | 179                | 181               |  |  |
| Units: Scores on a scale                     |                    |                   |  |  |
| least squares mean (confidence interval 95%) |                    |                   |  |  |
| Week 4                                       | 5.1 (4.3 to 6.0)   | 4.2 (3.4 to 5.1)  |  |  |
| Week 6                                       | 6.8 (5.9 to 7.6)   | 5.9 (5.0 to 6.7)  |  |  |
| Week 8                                       | 7.8 (6.9 to 8.7)   | 6.7 (5.8 to 7.5)  |  |  |
| Week 12                                      | 8.6 (7.6 to 9.5)   | 7.7 (6.7 to 8.6)  |  |  |
| Week 16                                      | 9.0 (7.9 to 10.1)  | 8.3 (7.2 to 9.5)  |  |  |
| Week 18                                      | 9.2 (8.0 to 10.3)  | 9.2 (8.0 to 10.3) |  |  |
| Week 20                                      | 9.6 (8.4 to 10.8)  | 9.4 (8.2 to 10.6) |  |  |
| Week 24                                      | 10.0 (8.8 to 11.2) | 8.7 (7.5 to 9.9)  |  |  |
| Week 28                                      | 9.8 (8.6 to 11.1)  | 9.4 (8.2 to 10.6) |  |  |
| Week 32                                      | 10.3 (9.1 to 11.5) | 8.9 (7.7 to 10.1) |  |  |
| Week 36                                      | 9.6 (8.4 to 10.9)  | 9.4 (8.2 to 10.7) |  |  |

|          |                    |                   |  |  |
|----------|--------------------|-------------------|--|--|
| Week 40  | 9.9 (8.7 to 11.2)  | 9.2 (7.9 to 10.4) |  |  |
| Week 44  | 10.6 (9.3 to 11.8) | 9.5 (8.3 to 10.8) |  |  |
| Week 48  | 10.1 (8.8 to 11.3) | 9.6 (8.3 to 10.9) |  |  |
| Week 52  | 10.6 (9.3 to 11.9) | 9.4 (8.1 to 10.7) |  |  |
| Week 56  | 10.7 (9.3 to 12.0) | 9.5 (8.2 to 10.9) |  |  |
| Week 60  | 10.5 (9.1 to 11.9) | 9.3 (8.0 to 10.7) |  |  |
| Week 64  | 11.0 (9.7 to 12.3) | 9.5 (8.2 to 10.8) |  |  |
| Week 68  | 11.0 (9.6 to 12.3) | 9.5 (8.2 to 10.8) |  |  |
| Week 72  | 11.0 (9.6 to 12.3) | 9.4 (8.1 to 10.8) |  |  |
| Week 76  | 10.5 (9.2 to 11.8) | 9.8 (8.4 to 11.1) |  |  |
| Week 80  | 10.2 (8.9 to 11.6) | 9.4 (8.1 to 10.8) |  |  |
| Week 84  | 10.9 (9.4 to 12.4) | 8.9 (7.4 to 10.4) |  |  |
| Week 88  | 10.7 (9.1 to 12.4) | 8.6 (7.0 to 10.2) |  |  |
| Week 92  | 10.7 (9.1 to 12.2) | 9.3 (7.7 to 10.8) |  |  |
| Week 96  | 10.7 (9.1 to 12.3) | 8.5 (6.8 to 10.1) |  |  |
| Week 100 | 10.9 (9.3 to 12.6) | 8.4 (6.7 to 10.1) |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | BCVA at Week 52                      |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other <sup>[9]</sup>                 |
| Parameter estimate                      | LS mean difference                   |
| Point estimate                          | 1.2                                  |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -0.6                                 |
| upper limit                             | 3.1                                  |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 0.94                                 |

Notes:

[9] - Treatment Difference

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | BCVA at Week 100                     |
| Comparison groups                 | Brolucizumab 6 mg v Aflibercept 2 mg |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 360                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other <sup>[10]</sup>      |
| Parameter estimate                      | LS mean difference         |
| Point estimate                          | 2.6                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.2                        |
| upper limit                             | 4.9                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 1.21                       |

Notes:

[10] - Treatment Difference

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### Secondary: Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 4 to Week 52/100 for the study eye

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|                 |                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 4 to Week 52/100 for the study eye |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. For each participants, this endpoint was defined as the mean change from baseline to the average value over the periods: Week 4 through Week 52, Week 4 through Week 100. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, period Week 4 through Week 52, period Week 4 through Week 100

---

| End point values                             | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|----------------------------------------------|-------------------|------------------|--|--|
| Subject group type                           | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed                  | 179               | 181              |  |  |
| Units: Scores on a scale                     |                   |                  |  |  |
| least squares mean (confidence interval 95%) |                   |                  |  |  |
| period Week 4 through Week 52                | 9.1 (8.2 to 10.1) | 8.4 (7.4 to 9.3) |  |  |
| period Week 4 through Week 100               | 9.8 (8.8 to 10.9) | 8.7 (7.7 to 9.8) |  |  |

## Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | BCVA over period Week 4 through Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg     |
| Number of subjects included in analysis | 360                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other <sup>[11]</sup>                    |
| Parameter estimate                      | LS mean difference                       |
| Point estimate                          | 1.1                                      |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.4                                     |
| upper limit                             | 2.6                                      |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 0.78                                     |

Notes:

[11] - Treatment difference

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>       | BCVA over period Week 4 through Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg    |
| Number of subjects included in analysis | 360                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | other <sup>[12]</sup>                   |
| Parameter estimate                      | LS mean difference                      |
| Point estimate                          | 0.8                                     |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.6                                    |
| upper limit                             | 2.1                                     |
| Variability estimate                    | Standard error of the mean              |
| Dispersion value                        | 0.7                                     |

Notes:

[12] - Treatment difference

### **Secondary: Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 20 to Week 52/100 and Week 28 to Week 52/100 for the study eye**

|                 |                                                                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 20 to Week 52/100 and Week 28 to Week 52/100 for the study eye |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. For each participants, this endpoint was defined as the mean change from baseline to the average value over the periods: Week 20 through Week 52, Week 20 through Week 100, Week 28 through Week 52, Week 28 through Week 100. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, period Week 20 through Week 52, period Week 20 through Week 100, period Week 28 through Week 52, period Week 28 through Week 100

| End point values                             | Brolucizumab 6 mg  | Aflibercept 2 mg  |  |  |
|----------------------------------------------|--------------------|-------------------|--|--|
| Subject group type                           | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed                  | 179                | 181               |  |  |
| Units: Scores on a scale                     |                    |                   |  |  |
| least squares mean (confidence interval 95%) |                    |                   |  |  |
| period Week 20 through Week 52               | 10.1 (8.9 to 11.2) | 9.3 (8.1 to 10.4) |  |  |
| period Week 20 through Week 100              | 10.4 (9.2 to 11.7) | 9.2 (8.0 to 10.4) |  |  |
| period Week 28 through Week 52               | 10.1 (9.0 to 11.3) | 9.4 (8.2 to 10.5) |  |  |
| period Week 28 through Week 100              | 10.5 (9.3 to 11.7) | 9.2 (8.0 to 10.5) |  |  |

## Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Statistical analysis title              | BCVA over period Week 20 through Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg     |
| Number of subjects included in analysis | 360                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other <sup>[13]</sup>                    |
| Parameter estimate                      | LS mean difference                       |
| Point estimate                          | 0.8                                      |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -0.9                                     |
| upper limit                             | 2.4                                      |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 0.83                                     |

Notes:

[13] - Treatment difference

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Statistical analysis title              | BCVA over period Week 28 through Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg     |
| Number of subjects included in analysis | 360                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other <sup>[14]</sup>                    |
| Parameter estimate                      | LS mean difference                       |
| Point estimate                          | 0.8                                      |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.9                       |
| upper limit          | 2.5                        |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.85                       |

Notes:

[14] - Treatment difference

|                                         |                                           |
|-----------------------------------------|-------------------------------------------|
| <b>Statistical analysis title</b>       | BCVA over period Week 20 through Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg      |
| Number of subjects included in analysis | 360                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | other <sup>[15]</sup>                     |
| Parameter estimate                      | LS mean difference                        |
| Point estimate                          | 1.2                                       |
| Confidence interval                     |                                           |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -0.5                                      |
| upper limit                             | 2.9                                       |
| Variability estimate                    | Standard error of the mean                |
| Dispersion value                        | 0.87                                      |

Notes:

[15] - Treatment difference

|                                         |                                           |
|-----------------------------------------|-------------------------------------------|
| <b>Statistical analysis title</b>       | BCVA over period Week 28 through Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg      |
| Number of subjects included in analysis | 360                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | other <sup>[16]</sup>                     |
| Parameter estimate                      | LS mean difference                        |
| Point estimate                          | 1.3                                       |
| Confidence interval                     |                                           |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -0.5                                      |
| upper limit                             | 3                                         |
| Variability estimate                    | Standard error of the mean                |
| Dispersion value                        | 0.89                                      |

Notes:

[16] - Treatment difference

## **Secondary: Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 88 to 100 for the study eye**

|                 |                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Average mean change from Baseline in Best Corrected Visual Acuity (BCVA) over the period Week 88 to 100 for the study eye |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|

**End point description:**

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. For each participants, this endpoint was defined as the mean change from baseline to the average value over the period Week 88 through Week 100. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

**End point timeframe:**

Baseline, period Week 88 through Week 100

| End point values                             | Brolucizumab 6 mg  | Aflibercept 2 mg  |  |  |
|----------------------------------------------|--------------------|-------------------|--|--|
| Subject group type                           | Reporting group    | Reporting group   |  |  |
| Number of subjects analysed                  | 179                | 181               |  |  |
| Units: Scores on a scale                     |                    |                   |  |  |
| least squares mean (confidence interval 95%) | 10.8 (9.2 to 12.3) | 8.7 (7.1 to 10.2) |  |  |

**Statistical analyses**

|                                         |                                           |
|-----------------------------------------|-------------------------------------------|
| <b>Statistical analysis title</b>       | BCVA over period Week 88 through Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg      |
| Number of subjects included in analysis | 360                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | other <sup>[17]</sup>                     |
| Parameter estimate                      | LS mean difference                        |
| Point estimate                          | 2.1                                       |
| Confidence interval                     |                                           |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -0.1                                      |
| upper limit                             | 4.3                                       |
| Variability estimate                    | Standard error of the mean                |
| Dispersion value                        | 1.12                                      |

**Notes:**

[17] - Treatment difference

**Secondary: Percentage of participants who gained  $\geq 5$  letters in BCVA from Baseline or reached BCVA  $\geq 84$  letters at each post-baseline visit for the study eye**

|                 |                                                                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants who gained $\geq 5$ letters in BCVA from Baseline or reached BCVA $\geq 84$ letters at each post-baseline visit for the study eye |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|

**End point description:**

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity

testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 4                            | 49.2 (41.6 to 56.7) | 46.4 (39.0 to 54.0) |  |  |
| Week 6                            | 62.0 (54.5 to 69.1) | 62.4 (54.9 to 69.5) |  |  |
| Week 8                            | 67.6 (60.2 to 74.4) | 63.5 (56.1 to 70.5) |  |  |
| Week 12                           | 70.9 (63.7 to 77.5) | 73.5 (66.4 to 79.8) |  |  |
| Week 16                           | 71.5 (64.3 to 78.0) | 73.5 (66.4 to 79.8) |  |  |
| Week 18                           | 77.7 (70.8 to 83.5) | 77.9 (71.1 to 83.7) |  |  |
| Week 20                           | 79.3 (72.7 to 85.0) | 76.2 (69.4 to 82.2) |  |  |
| Week 24                           | 79.9 (73.3 to 85.5) | 77.9 (71.1 to 83.7) |  |  |
| Week 28                           | 75.4 (68.4 to 81.5) | 77.9 (71.1 to 83.7) |  |  |
| Week 32                           | 77.1 (70.2 to 83.0) | 80.7 (74.1 to 86.1) |  |  |
| Week 36                           | 74.3 (67.2 to 80.5) | 80.7 (74.1 to 86.1) |  |  |
| Week 40                           | 74.9 (67.8 to 81.0) | 79.6 (72.9 to 85.2) |  |  |
| Week 44                           | 74.3 (67.2 to 80.5) | 80.7 (74.1 to 86.1) |  |  |
| Week 48                           | 76.0 (69.0 to 82.0) | 79.0 (72.3 to 84.7) |  |  |
| Week 52                           | 77.7 (70.8 to 83.5) | 79.0 (72.3 to 84.7) |  |  |
| Week 56                           | 77.7 (70.8 to 83.5) | 80.7 (74.1 to 86.1) |  |  |
| Week 60                           | 76.0 (69.0 to 82.0) | 79.0 (72.3 to 84.7) |  |  |
| Week 64                           | 78.2 (71.4 to 84.0) | 79.0 (72.3 to 84.7) |  |  |
| Week 68                           | 77.7 (70.8 to 83.5) | 76.8 (70.0 to 82.7) |  |  |
| Week 72                           | 79.9 (73.3 to 85.5) | 77.3 (70.6 to 83.2) |  |  |

|          |                     |                     |  |  |
|----------|---------------------|---------------------|--|--|
| Week 76  | 74.3 (67.2 to 80.5) | 77.3 (70.6 to 83.2) |  |  |
| Week 80  | 74.3 (67.2 to 80.5) | 75.7 (68.8 to 81.7) |  |  |
| Week 84  | 78.2 (71.4 to 84.0) | 73.5 (66.4 to 79.8) |  |  |
| Week 88  | 77.7 (70.8 to 83.5) | 75.7 (68.8 to 81.7) |  |  |
| Week 92  | 79.3 (72.7 to 85.0) | 74.0 (67.0 to 80.3) |  |  |
| Week 96  | 78.8 (72.0 to 84.5) | 73.5 (66.4 to 79.8) |  |  |
| Week 100 | 77.1 (70.2 to 83.0) | 73.5 (66.4 to 79.8) |  |  |

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Gain of $\geq 5$ letters in BCVA at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg         |
| Number of subjects included in analysis | 360                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[18]</sup>                        |
| Parameter estimate                      | Clopper-Pearson exact method                 |
| Point estimate                          | 5.4                                          |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -3.9                                         |
| upper limit                             | 14.5                                         |

Notes:

[18] - Treatment difference

|                                         |                                             |
|-----------------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b>       | Gain of $\geq 5$ letters in BCVA at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg        |
| Number of subjects included in analysis | 360                                         |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | other <sup>[19]</sup>                       |
| Parameter estimate                      | Clopper-Pearson exact method                |
| Point estimate                          | 0.4                                         |
| Confidence interval                     |                                             |
| level                                   | 95 %                                        |
| sides                                   | 2-sided                                     |
| lower limit                             | -7.6                                        |
| upper limit                             | 8.9                                         |

Notes:

[19] - Treatment difference

### Secondary: Percentage of participants who gained $\geq 10$ letters in BCVA from Baseline or reached BCVA $\geq 84$ letters at each post-baseline visit for the study eye

|                 |                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants who gained $\geq 10$ letters in BCVA from Baseline or reached BCVA $\geq 84$ letters at each post- |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

## End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

## End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 4                            | 22.9 (17.0 to 29.8) | 23.8 (17.8 to 30.6) |  |  |
| Week 6                            | 34.6 (27.7 to 42.1) | 31.5 (24.8 to 38.8) |  |  |
| Week 8                            | 39.7 (32.4 to 47.2) | 36.5 (29.5 to 43.9) |  |  |
| Week 12                           | 43.0 (35.7 to 50.6) | 45.9 (39.4 to 53.4) |  |  |
| Week 16                           | 44.1 (36.7 to 51.7) | 49.7 (42.2 to 57.2) |  |  |
| Week 18                           | 47.5 (40.0 to 55.1) | 53.0 (45.5 to 60.5) |  |  |
| Week 20                           | 53.1 (45.5 to 60.6) | 56.9 (49.4 to 64.2) |  |  |
| Week 24                           | 56.4 (48.8 to 63.8) | 53.6 (46.0 to 61.0) |  |  |
| Week 28                           | 55.3 (47.7 to 62.7) | 55.2 (47.7 to 62.6) |  |  |
| Week 32                           | 58.7 (51.1 to 66.0) | 51.9 (44.4 to 59.4) |  |  |
| Week 36                           | 57.5 (49.9 to 64.9) | 55.2 (47.7 to 62.6) |  |  |
| Week 40                           | 58.1 (50.5 to 65.4) | 52.5 (44.9 to 59.9) |  |  |
| Week 44                           | 61.5 (53.9 to 68.6) | 56.9 (49.4 to 64.2) |  |  |
| Week 48                           | 60.9 (53.3 to 68.1) | 53.0 (45.5 to 60.5) |  |  |
| Week 52                           | 61.5 (53.9 to 68.6) | 58.6 (51.0 to 65.8) |  |  |
| Week 56                           | 62.0 (54.5 to 69.1) | 54.1 (46.6 to 61.6) |  |  |
| Week 60                           | 61.5 (53.9 to 68.6) | 54.7 (47.1 to 62.1) |  |  |
| Week 64                           | 63.7 (56.2 to 70.7) | 56.9 (49.4 to 64.2) |  |  |

|          |                     |                     |  |  |
|----------|---------------------|---------------------|--|--|
| Week 68  | 62.0 (54.5 to 69.1) | 57.5 (49.9 to 64.8) |  |  |
| Week 72  | 63.7 (56.2 to 70.7) | 56.4 (48.8 to 63.7) |  |  |
| Week 76  | 60.9 (53.3 to 68.1) | 56.9 (49.4 to 64.2) |  |  |
| Week 80  | 57.5 (49.9 to 64.9) | 55.8 (48.2 to 63.2) |  |  |
| Week 84  | 63.7 (56.2 to 70.7) | 58.6 (51.0 to 65.8) |  |  |
| Week 88  | 61.5 (53.9 to 68.6) | 58.0 (50.5 to 65.3) |  |  |
| Week 92  | 63.7 (56.2 to 70.7) | 58.6 (51.0 to 65.8) |  |  |
| Week 96  | 62.6 (55.0 to 69.7) | 56.9 (49.4 to 64.2) |  |  |
| Week 100 | 61.5 (53.9 to 68.6) | 54.1 (46.6 to 61.6) |  |  |

### Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Gain of $\geq 10$ letters in BCVA at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg          |
| Number of subjects included in analysis | 360                                           |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | other <sup>[20]</sup>                         |
| Parameter estimate                      | Clopper-Pearson exact method                  |
| Point estimate                          | 9.9                                           |
| Confidence interval                     |                                               |
| level                                   | 95 %                                          |
| sides                                   | 2-sided                                       |
| lower limit                             | -0.4                                          |
| upper limit                             | 19.4                                          |

Notes:

[20] - Treatment difference

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Gain of $\geq 10$ letters in BCVA at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg         |
| Number of subjects included in analysis | 360                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[21]</sup>                        |
| Parameter estimate                      | Clopper-Pearson exact method                 |
| Point estimate                          | 5.4                                          |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -3.9                                         |
| upper limit                             | 14.7                                         |

Notes:

[21] - Treatment difference

**Secondary: Percentage of participants who gained  $\geq 15$  letters in BCVA from Baseline or reached BCVA  $\geq 84$  letters at each post-baseline visit for the study eye**

|                 |                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants who gained $\geq 15$ letters in BCVA from Baseline or reached BCVA $\geq 84$ letters at each post-baseline visit for the study eye |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 4                            | 12.3 (7.9 to 18.0)  | 9.4 (5.6 to 14.6)   |  |  |
| Week 6                            | 13.4 (8.8 to 19.3)  | 13.8 (9.1 to 19.7)  |  |  |
| Week 8                            | 25.1 (19.0 to 32.2) | 16.0 (11.0 to 22.2) |  |  |
| Week 12                           | 25.1 (19.0 to 32.2) | 22.1 (16.3 to 28.9) |  |  |
| Week 16                           | 33.5 (26.7 to 40.9) | 25.4 (19.2 to 32.4) |  |  |
| Week 18                           | 31.8 (25.1 to 39.2) | 33.1 (26.3 to 40.5) |  |  |
| Week 20                           | 34.6 (27.7 to 42.1) | 32.6 (25.8 to 39.9) |  |  |
| Week 24                           | 41.9 (34.6 to 49.5) | 30.9 (24.3 to 38.2) |  |  |
| Week 28                           | 40.2 (33.0 to 47.8) | 37.0 (30.0 to 44.5) |  |  |
| Week 32                           | 44.1 (36.7 to 51.7) | 30.4 (23.8 to 37.6) |  |  |
| Week 36                           | 45.3 (37.8 to 52.8) | 32.6 (25.8 to 39.9) |  |  |
| Week 40                           | 44.7 (37.3 to 52.3) | 31.5 (24.8 to 38.8) |  |  |
| Week 44                           | 50.3 (42.7 to 57.8) | 35.4 (28.4 to 42.8) |  |  |
| Week 48                           | 41.9 (34.6 to 49.5) | 37.0 (30.0 to 44.5) |  |  |
| Week 52                           | 46.4 (38.9 to 54.0) | 37.6 (30.5 to 45.1) |  |  |

|          |                     |                     |  |  |
|----------|---------------------|---------------------|--|--|
| Week 56  | 46.4 (38.9 to 54.0) | 35.9 (28.9 to 43.4) |  |  |
| Week 60  | 46.9 (39.4 to 54.5) | 38.7 (31.5 to 46.2) |  |  |
| Week 64  | 50.3 (42.7 to 57.8) | 36.5 (29.5 to 43.9) |  |  |
| Week 68  | 48.6 (41.1 to 56.2) | 35.9 (28.9 to 43.4) |  |  |
| Week 72  | 48.0 (40.5 to 55.6) | 35.4 (28.4 to 42.8) |  |  |
| Week 76  | 46.4 (38.9 to 54.0) | 40.9 (33.6 to 48.4) |  |  |
| Week 80  | 43.6 (36.2 to 51.2) | 37.6 (30.5 to 45.1) |  |  |
| Week 84  | 46.4 (38.9 to 54.0) | 37.0 (30.0 to 44.5) |  |  |
| Week 88  | 47.5 (40.0 to 55.1) | 40.9 (33.6 to 48.4) |  |  |
| Week 92  | 44.7 (37.3 to 52.3) | 40.3 (33.1 to 47.9) |  |  |
| Week 96  | 46.9 (39.4 to 54.5) | 38.1 (31.0 to 45.6) |  |  |
| Week 100 | 49.7 (42.2 to 57.3) | 37.6 (30.5 to 45.1) |  |  |

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Gain of $\geq 15$ letters in BCVA at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg         |
| Number of subjects included in analysis | 360                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[22]</sup>                        |
| Parameter estimate                      | Clopper-Pearson exact method                 |
| Point estimate                          | 9.6                                          |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -0.4                                         |
| upper limit                             | 20.2                                         |

Notes:

[22] - Treatment difference

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Gain of $\geq 15$ letters in BCVA at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg          |
| Number of subjects included in analysis | 360                                           |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | other <sup>[23]</sup>                         |
| Parameter estimate                      | Clopper-Pearson exact method                  |
| Point estimate                          | 13.6                                          |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 3.3     |
| upper limit         | 23.5    |

Notes:

[23] - Treatment difference

### Secondary: Percentage of participants who lost $\geq 5$ ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

|                 |                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants who lost $\geq 5$ ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------------|-------------------|------------------|--|--|
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 179               | 181              |  |  |
| Units: Percentage of Participants |                   |                  |  |  |
| number (confidence interval 95%)  |                   |                  |  |  |
| Week 4                            | 3.4 (1.2 to 7.2)  | 4.4 (1.9 to 8.5) |  |  |
| Week 6                            | 1.7 (0.3 to 4.8)  | 3.3 (1.2 to 7.1) |  |  |
| Week 8                            | 1.1 (0.1 to 4.0)  | 2.8 (0.9 to 6.3) |  |  |
| Week 12                           | 1.1 (0.1 to 4.0)  | 2.2 (0.6 to 5.6) |  |  |
| Week 16                           | 0.6 (0.0 to 3.1)  | 2.2 (0.6 to 5.6) |  |  |
| Week 18                           | 1.1 (0.1 to 4.0)  | 1.1 (0.1 to 3.9) |  |  |
| Week 20                           | 2.2 (0.6 to 5.6)  | 2.8 (0.9 to 6.3) |  |  |
| Week 24                           | 1.7 (0.3 to 4.8)  | 3.3 (1.2 to 7.1) |  |  |
| Week 28                           | 1.7 (0.3 to 4.8)  | 2.2 (0.6 to 5.6) |  |  |
| Week 32                           | 2.2 (0.6 to 5.6)  | 2.2 (0.6 to 5.6) |  |  |
| Week 36                           | 4.5 (1.9 to 8.6)  | 1.1 (0.1 to 3.9) |  |  |
| Week 40                           | 3.9 (1.6 to 7.9)  | 2.2 (0.6 to 5.6) |  |  |
| Week 44                           | 2.8 (0.9 to 6.4)  | 2.2 (0.6 to 5.6) |  |  |
| Week 48                           | 2.8 (0.9 to 6.4)  | 2.8 (0.9 to 6.3) |  |  |
| Week 52                           | 3.4 (1.2 to 7.2)  | 3.3 (1.2 to 7.1) |  |  |
| Week 56                           | 5.0 (2.3 to 9.3)  | 3.3 (1.2 to 7.1) |  |  |
| Week 60                           | 3.9 (1.6 to 7.9)  | 4.4 (1.9 to 8.5) |  |  |

|          |                  |                   |  |  |
|----------|------------------|-------------------|--|--|
| Week 64  | 2.8 (0.9 to 6.4) | 3.3 (1.2 to 7.1)  |  |  |
| Week 68  | 3.9 (1.6 to 7.9) | 2.8 (0.9 to 6.3)  |  |  |
| Week 72  | 4.5 (1.9 to 8.6) | 5.0 (2.3 to 9.2)  |  |  |
| Week 76  | 3.4 (1.2 to 7.2) | 4.4 (1.9 to 8.5)  |  |  |
| Week 80  | 2.8 (0.9 to 6.4) | 6.1 (3.1 to 10.6) |  |  |
| Week 84  | 3.4 (1.2 to 7.2) | 7.7 (4.3 to 12.6) |  |  |
| Week 88  | 3.9 (1.6 to 7.9) | 7.2 (3.9 to 12.0) |  |  |
| Week 92  | 3.4 (1.2 to 7.2) | 6.6 (3.5 to 11.3) |  |  |
| Week 96  | 3.9 (1.6 to 7.9) | 7.2 (3.9 to 12.0) |  |  |
| Week 100 | 2.8 (0.9 to 6.4) | 8.3 (4.7 to 13.3) |  |  |

## Statistical analyses

|                                         |                                             |
|-----------------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b>       | Loss of $\geq 5$ letters in BCVA at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg        |
| Number of subjects included in analysis | 360                                         |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | other <sup>[24]</sup>                       |
| Parameter estimate                      | Clopper-Pearson exact method                |
| Point estimate                          | -0.4                                        |
| Confidence interval                     |                                             |
| level                                   | 95 %                                        |
| sides                                   | 2-sided                                     |
| lower limit                             | -4.2                                        |
| upper limit                             | 2.9                                         |

Notes:

[24] - Treatment difference

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Loss of $\geq 5$ letters in BCVA at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg         |
| Number of subjects included in analysis | 360                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[25]</sup>                        |
| Parameter estimate                      | Clopper-Pearson exact method                 |
| Point estimate                          | -6                                           |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -10.8                                        |
| upper limit                             | -1.7                                         |

Notes:

[25] - Treatment difference

## Secondary: Percentage of participants who lost $\geq 10$ ETDRS letters in Best

## Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

|                 |                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants who lost $\geq 10$ ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------------|-------------------|------------------|--|--|
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 179               | 181              |  |  |
| Units: Percentage of Participants |                   |                  |  |  |
| number (confidence interval 95%)  |                   |                  |  |  |
| Week 4                            | 999 (999 to 999)  | 1.1 (0.1 to 3.9) |  |  |
| Week 6                            | 1.1 (0.1 to 4.0)  | 0.6 (0.0 to 3.0) |  |  |
| Week 8                            | 1.1 (0.1 to 4.0)  | 999 (999 to 999) |  |  |
| Week 12                           | 999 (999 to 999)  | 0.6 (0.0 to 3.0) |  |  |
| Week 16                           | 0.6 (0.0 to 3.1)  | 999 (999 to 999) |  |  |
| Week 18                           | 1.1 (0.1 to 4.0)  | 999 (999 to 999) |  |  |
| Week 20                           | 1.7 (0.3 to 4.8)  | 999 (999 to 999) |  |  |
| Week 24                           | 1.7 (0.3 to 4.8)  | 1.1 (0.1 to 3.9) |  |  |
| Week 28                           | 1.7 (0.3 to 4.8)  | 999 (999 to 999) |  |  |
| Week 32                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 36                           | 3.4 (1.2 to 7.2)  | 999 (999 to 999) |  |  |
| Week 40                           | 2.8 (0.9 to 6.4)  | 999 (999 to 999) |  |  |
| Week 44                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 48                           | 2.2 (0.6 to 5.6)  | 0.6 (0.0 to 3.0) |  |  |
| Week 52                           | 2.2 (0.6 to 5.6)  | 2.2 (0.6 to 5.6) |  |  |
| Week 56                           | 2.2 (0.6 to 5.6)  | 1.1 (0.1 to 3.9) |  |  |
| Week 60                           | 1.7 (0.3 to 4.8)  | 1.7 (0.3 to 4.8) |  |  |
| Week 64                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 68                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 72                           | 2.2 (0.6 to 5.6)  | 1.7 (0.3 to 4.8) |  |  |

|          |                  |                   |  |  |
|----------|------------------|-------------------|--|--|
| Week 76  | 2.2 (0.6 to 5.6) | 0.6 (0.0 to 3.0)  |  |  |
| Week 80  | 1.7 (0.3 to 4.8) | 1.7 (0.3 to 4.8)  |  |  |
| Week 84  | 2.2 (0.6 to 5.6) | 4.4 (1.9 to 8.5)  |  |  |
| Week 88  | 2.8 (0.9 to 6.4) | 3.9 (1.6 to 7.8)  |  |  |
| Week 92  | 2.8 (0.9 to 6.3) | 2.8 (0.9 to 6.3)  |  |  |
| Week 96  | 2.2 (0.6 to 5.6) | 3.9 (1.6 to 7.8)  |  |  |
| Week 100 | 2.2 (0.6 to 5.6) | 6.1 (3.1 to 10.6) |  |  |

## Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Loss of $\geq 10$ letters in BCVA at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg         |
| Number of subjects included in analysis | 360                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[26]</sup>                        |
| Parameter estimate                      | Clopper-Pearson exact method                 |
| Point estimate                          | -0.2                                         |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -3.2                                         |
| upper limit                             | 2.4                                          |

Notes:

[26] - Treatment difference

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Loss of $\geq 10$ letters in BCVA at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg          |
| Number of subjects included in analysis | 360                                           |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | other <sup>[27]</sup>                         |
| Parameter estimate                      | Clopper-Pearson exact method                  |
| Point estimate                          | -4.1                                          |
| Confidence interval                     |                                               |
| level                                   | 95 %                                          |
| sides                                   | 2-sided                                       |
| lower limit                             | -8.4                                          |
| upper limit                             | -0.1                                          |

Notes:

[27] - Treatment difference

## Secondary: Percentage of participants who lost $\geq 15$ ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye

|                 |                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants who lost $\geq 15$ ETDRS letters in Best Corrected Visual Acuity (BCVA) from Baseline at each post-baseline visit for the study eye |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were

taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------------|-------------------|------------------|--|--|
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 179               | 181              |  |  |
| Units: Percentage of Participants |                   |                  |  |  |
| number (confidence interval 95%)  |                   |                  |  |  |
| Week 4                            | 999 (999 to 999)  | 0.6 (0.0 to 3.0) |  |  |
| Week 6                            | 1.1 (0.1 to 4.0)  | 999 (999 to 999) |  |  |
| Week 8                            | 0.6 (0.0 to 3.1)  | 999 (999 to 999) |  |  |
| Week 12                           | 999 (999 to 999)  | 0.6 (0.0 to 3.0) |  |  |
| Week 16                           | 0.6 (0.0 to 3.1)  | 999 (999 to 999) |  |  |
| Week 18                           | 1.1 (0.1 to 4.0)  | 999 (999 to 999) |  |  |
| Week 20                           | 1.7 (0.3 to 4.8)  | 999 (999 to 999) |  |  |
| Week 24                           | 1.1 (0.1 to 4.0)  | 0.6 (0.0 to 3.0) |  |  |
| Week 28                           | 1.7 (0.3 to 4.8)  | 999 (999 to 999) |  |  |
| Week 32                           | 1.7 (0.3 to 4.8)  | 999 (999 to 999) |  |  |
| Week 36                           | 2.8 (0.9 to 6.4)  | 999 (999 to 999) |  |  |
| Week 40                           | 2.2 (0.6 to 5.6)  | 999 (999 to 999) |  |  |
| Week 44                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 48                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 52                           | 1.1 (0.1 to 4.0)  | 1.7 (0.3 to 4.8) |  |  |
| Week 56                           | 1.7 (0.3 to 4.8)  | 1.1 (0.1 to 3.9) |  |  |
| Week 60                           | 1.7 (0.3 to 4.8)  | 1.7 (0.3 to 4.8) |  |  |
| Week 64                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 68                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 72                           | 2.2 (0.6 to 5.6)  | 1.1 (0.1 to 3.9) |  |  |
| Week 76                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 80                           | 1.7 (0.3 to 4.8)  | 0.6 (0.0 to 3.0) |  |  |
| Week 84                           | 1.7 (0.3 to 4.8)  | 2.2 (0.6 to 5.6) |  |  |
| Week 88                           | 1.7 (0.3 to 4.8)  | 2.2 (0.6 to 5.6) |  |  |
| Week 92                           | 2.2 (0.6 to 5.6)  | 2.2 (0.6 to 5.6) |  |  |
| Week 96                           | 2.2 (0.6 to 5.6)  | 2.2 (0.6 to 5.6) |  |  |

|          |                  |                  |  |  |
|----------|------------------|------------------|--|--|
| Week 100 | 2.2 (0.6 to 5.6) | 3.3 (1.2 to 7.1) |  |  |
|----------|------------------|------------------|--|--|

## Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Loss of $\geq 15$ letters in BCVA at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg         |
| Number of subjects included in analysis | 360                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[28]</sup>                        |
| Parameter estimate                      | Clopper-Pearson exact method                 |
| Point estimate                          | -0.7                                         |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -3.2                                         |
| upper limit                             | 1.6                                          |

Notes:

[28] - Treatment difference

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | Loss of $\geq 15$ letters in BCVA at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg          |
| Number of subjects included in analysis | 360                                           |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | other <sup>[29]</sup>                         |
| Parameter estimate                      | Clopper-Pearson exact method                  |
| Point estimate                          | -1.3                                          |
| Confidence interval                     |                                               |
| level                                   | 95 %                                          |
| sides                                   | 2-sided                                       |
| lower limit                             | -4.8                                          |
| upper limit                             | 2                                             |

Notes:

[29] - Treatment difference

## Secondary: Percentage of participants with an Absolute Best Corrected Visual Acuity (BCVA) $\geq 73$ ETDRS letters at each post-baseline visit for the study eye

|                 |                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants with an Absolute Best Corrected Visual Acuity (BCVA) $\geq 73$ ETDRS letters at each post-baseline visit for the study eye |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Best Corrected Visual Acuity (BCVA) was assessed during all study visits using best correction determined from protocol refraction at a starting test distance of 4 meters. VA measurements were taken in a sitting position using Early Treatment Diabetic Retinopathy Study (ETDRS)-like visual acuity testing charts. The overall BCVA score (number of letters read correctly by the patient) was calculated using the BCVA worksheet 0-100 letter score, with higher score indicating improvement in acuity. A positive change from baseline is a favorable outcome. BCVA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 4                            | 55.3 (47.7 to 62.7) | 42.5 (35.2 to 50.1) |  |  |
| Week 6                            | 64.8 (57.3 to 71.8) | 49.7 (42.2 to 57.2) |  |  |
| Week 8                            | 66.5 (59.1 to 73.3) | 50.8 (43.3 to 58.3) |  |  |
| Week 12                           | 66.5 (59.1 to 73.3) | 59.7 (52.1 to 66.9) |  |  |
| Week 16                           | 69.8 (62.5 to 76.5) | 60.8 (53.3 to 67.9) |  |  |
| Week 18                           | 71.5 (64.3 to 78.0) | 64.6 (57.2 to 71.6) |  |  |
| Week 20                           | 71.5 (64.3 to 78.0) | 61.3 (53.8 to 68.5) |  |  |
| Week 24                           | 73.2 (66.1 to 79.5) | 60.2 (52.7 to 67.4) |  |  |
| Week 28                           | 72.6 (65.5 to 79.0) | 61.9 (54.4 to 69.0) |  |  |
| Week 32                           | 73.7 (66.7 to 80.0) | 59.1 (51.6 to 66.4) |  |  |
| Week 36                           | 70.4 (63.1 to 77.0) | 65.2 (57.8 to 72.1) |  |  |
| Week 40                           | 69.8 (62.5 to 76.5) | 60.2 (52.7 to 67.4) |  |  |
| Week 44                           | 73.7 (66.7 to 80.0) | 63.5 (56.1 to 70.5) |  |  |
| Week 48                           | 70.9 (63.7 to 77.5) | 61.3 (53.8 to 68.5) |  |  |
| Week 52                           | 73.7 (66.7 to 80.0) | 64.6 (57.2 to 71.6) |  |  |
| Week 56                           | 72.6 (65.5 to 79.0) | 66.9 (59.5 to 73.7) |  |  |
| Week 60                           | 70.9 (63.7 to 77.5) | 66.9 (59.5 to 73.7) |  |  |
| Week 64                           | 74.3 (67.2 to 80.5) | 68.5 (61.2 to 75.2) |  |  |
| Week 68                           | 71.5 (64.3 to 78.0) | 66.3 (58.9 to 73.1) |  |  |
| Week 72                           | 73.7 (66.7 to 80.0) | 65.2 (57.8 to 72.1) |  |  |
| Week 76                           | 72.6 (65.5 to 79.0) | 66.9 (59.5 to 73.7) |  |  |
| Week 80                           | 70.9 (63.7 to 77.5) | 64.1 (56.6 to 71.1) |  |  |
| Week 84                           | 70.9 (63.7 to 77.5) | 65.2 (57.8 to 72.1) |  |  |

|          |                     |                     |  |  |
|----------|---------------------|---------------------|--|--|
| Week 88  | 72.6 (65.5 to 79.0) | 63.5 (56.1 to 70.5) |  |  |
| Week 92  | 71.5 (64.3 to 78.0) | 63.5 (56.1 to 70.5) |  |  |
| Week 96  | 70.4 (63.1 to 77.0) | 62.4 (54.9 to 69.5) |  |  |
| Week 100 | 70.9 (63.7 to 77.5) | 62.4 (54.9 to 69.5) |  |  |

### Statistical analyses

|                                         |                                             |
|-----------------------------------------|---------------------------------------------|
| <b>Statistical analysis title</b>       | Absolute BCVA $\geq$ 73 letters at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg        |
| Number of subjects included in analysis | 360                                         |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | other <sup>[30]</sup>                       |
| Parameter estimate                      | Clopper-Pearson exact method                |
| Point estimate                          | 3.6                                         |
| Confidence interval                     |                                             |
| level                                   | 95 %                                        |
| sides                                   | 2-sided                                     |
| lower limit                             | -5.4                                        |
| upper limit                             | 12.6                                        |

Notes:

[30] - Treatment difference

|                                         |                                            |
|-----------------------------------------|--------------------------------------------|
| <b>Statistical analysis title</b>       | Absolute BCVA $\geq$ 73 letters at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg       |
| Number of subjects included in analysis | 360                                        |
| Analysis specification                  | Pre-specified                              |
| Analysis type                           | other <sup>[31]</sup>                      |
| Parameter estimate                      | Clopper-Pearson exact method               |
| Point estimate                          | 3.5                                        |
| Confidence interval                     |                                            |
| level                                   | 95 %                                       |
| sides                                   | 2-sided                                    |
| lower limit                             | -4.9                                       |
| upper limit                             | 12                                         |

Notes:

[31] - Treatment difference

### Secondary: Mean change from Baseline in Central Subfield Thickness (CSFT) at each post-baseline visit for the study eye

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline in Central Subfield Thickness (CSFT) at each post-baseline visit for the study eye |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

The thickness of the retina was measured using Spectral Domain (SD) optical coherence tomography (OCT) equipment (SD-OCT) and reported as a difference, in micrometers. a negative change from baseline indicates a reduction in thickness, whereas a positive change from baseline indicates an increase. An increase in thickness may indicate a progression of the underlying disease. CSFT assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were

censored and replaced by the last value prior to start of this alternative treatment.

|                                                                                                                                                                                                                                                           |           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                                                                                                                                            | Secondary |
| End point timeframe:                                                                                                                                                                                                                                      |           |
| Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100 |           |

| End point values                     | Brolucizumab 6 mg       | Aflibercept 2 mg       |  |  |
|--------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                   | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed          | 179                     | 181                    |  |  |
| Units: Micrometers                   |                         |                        |  |  |
| arithmetic mean (standard deviation) |                         |                        |  |  |
| Week 4                               | -128.2 ( $\pm$ 131.47)  | -113.9 ( $\pm$ 123.20) |  |  |
| Week 6                               | -136.9 ( $\pm$ 135.57)  | -126.0 ( $\pm$ 124.82) |  |  |
| Week 8                               | -155.4 ( $\pm$ 139.09)  | -130.8 ( $\pm$ 124.71) |  |  |
| Week 12                              | -160.8 ( $\pm$ 137.23)  | -137.9 ( $\pm$ 132.30) |  |  |
| Week 16                              | -179.1 ( $\pm$ 137.26)  | -145.3 ( $\pm$ 132.63) |  |  |
| Week 18                              | -175.8 ( $\pm$ 139.10)  | -149.0 ( $\pm$ 132.28) |  |  |
| Week 20                              | -183.7 ( $\pm$ 139.76)  | -151.0 ( $\pm$ 130.98) |  |  |
| Week 24                              | -183.3 ( $\pm$ 143.14)  | -134.0 ( $\pm$ 136.67) |  |  |
| Week 28                              | -192.0 ( $\pm$ 145.85)  | -161.4 ( $\pm$ 131.27) |  |  |
| Week 32                              | -178.6 ( $\pm$ 138.5)   | -144.9 ( $\pm$ 135.93) |  |  |
| Week 36                              | -163.5 ( $\pm$ 144.34)  | -162.9 ( $\pm$ 135.19) |  |  |
| Week 40                              | -183.3 ( $\pm$ 139.84)  | -149.9 ( $\pm$ 132.66) |  |  |
| Week 44                              | -193.3 ( $\pm$ 144.12)  | -163.5 ( $\pm$ 133.01) |  |  |
| Week 48                              | -172.8 ( $\pm$ 141.83)  | -154.6 ( $\pm$ 130.54) |  |  |
| Week 52                              | -196.5 ( $\pm$ 144.44)  | -165.0 ( $\pm$ 134.77) |  |  |
| Week 56                              | -191.08 ( $\pm$ 148.02) | -162.4 ( $\pm$ 132.53) |  |  |
| Week 60                              | -189.8 ( $\pm$ 147.93)  | -166.2 ( $\pm$ 132.61) |  |  |
| Week 64                              | -193.2 ( $\pm$ 143.36)  | -160.2 ( $\pm$ 137.83) |  |  |
| Week 68                              | -194.5 ( $\pm$ 141.47)  | -169.8 ( $\pm$ 143.97) |  |  |
| Week 72                              | -190.4 ( $\pm$ 142.25)  | -165.1 ( $\pm$ 141.38) |  |  |
| Week 76                              | -185.6 ( $\pm$ 143.68)  | -174.7 ( $\pm$ 138.70) |  |  |
| Week 80                              | -185.7 ( $\pm$ 145.52)  | -171.1 ( $\pm$ 138.53) |  |  |

|          |                   |                   |  |  |
|----------|-------------------|-------------------|--|--|
| Week 84  | -193.5 (± 142.53) | -175.1 (± 139.76) |  |  |
| Week 88  | -191.0 (± 141.29) | -172.2 (± 138.08) |  |  |
| Week 92  | -193.8 (± 142.07) | -180.1 (± 138.88) |  |  |
| Week 96  | -197.2 (± 144.29) | -170.2 (± 154.37) |  |  |
| Week 100 | -201.4 (± 142.90) | -173.9 (± 152.03) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Average mean change from Baseline in Central Subfield Thickness (CSFT) over the period Week 40 through Week 52 / Week 88 through Week 100 for the study eye

|                 |                                                                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Average mean change from Baseline in Central Subfield Thickness (CSFT) over the period Week 40 through Week 52 / Week 88 through Week 100 for the study eye |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The thickness of the retina was measured using Spectral Domain (SD) optical coherence tomography (OCT) equipment (SD-OCT) and reported as a difference, in micrometers. a negative change from baseline indicates a reduction in thickness, whereas a positive change from baseline indicates an increase. An increase in thickness may indicate a progression of the underlying disease. CSFT assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment. For each participants, this endpoint was derived as the average of the changes from Baseline to Weeks 40, 44, 48, 52. Then the same was derived over the period Week 88 through Week 100, considering the average of the changes from Baseline to Weeks 88, 92, 96, 100. This endpoint was only assessed in the year-2 analysis (Week 100).

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

End point timeframe:

Baseline, period Week 40 through Week 52, period Week 88 through Week 100

| End point values                             | Brolucizumab 6 mg         | Aflibercept 2 mg          |  |  |
|----------------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type                           | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed                  | 179                       | 181                       |  |  |
| Units: Micrometers                           |                           |                           |  |  |
| least squares mean (confidence interval 95%) |                           |                           |  |  |
| period Week 40 through Week 52               | -187.1 (-200.7 to -173.5) | -157.7 (-171.2 to -144.1) |  |  |
| period Week 88 through Week 100              | -196.6 (-210.9 to -182.3) | -173.4 (-187.6 to -159.1) |  |  |

## Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | CSFT over period Week 40 through Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg     |
| Number of subjects included in analysis | 360                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other <sup>[32]</sup>                    |
| P-value                                 | < 0.003                                  |
| Method                                  | ANOVA                                    |
| Parameter estimate                      | LS mean difference                       |
| Point estimate                          | -29.4                                    |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -48.6                                    |
| upper limit                             | -10.2                                    |
| Variability estimate                    | Standard error of the mean               |
| Dispersion value                        | 9.76                                     |

Notes:

[32] - Treatment difference

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | CSFT over period Week 40 through Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg     |
| Number of subjects included in analysis | 360                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | superiority                              |
| P-value                                 | = 0.001                                  |
| Method                                  | ANOVA                                    |

|                                         |                                           |
|-----------------------------------------|-------------------------------------------|
| <b>Statistical analysis title</b>       | CSFT over period Week 88 through Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg      |
| Number of subjects included in analysis | 360                                       |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | other <sup>[33]</sup>                     |
| Parameter estimate                      | LS mean difference                        |
| Point estimate                          | -23.2                                     |
| Confidence interval                     |                                           |
| level                                   | 95 %                                      |
| sides                                   | 2-sided                                   |
| lower limit                             | -43.5                                     |
| upper limit                             | -3                                        |
| Variability estimate                    | Standard error of the mean                |
| Dispersion value                        | 10.28                                     |

Notes:

[33] - Treatment difference

### Secondary: Average mean change from baseline in CSFT over the period Week 4 to Week 52 / 100 for the study eye

|                 |                                                                                                     |
|-----------------|-----------------------------------------------------------------------------------------------------|
| End point title | Average mean change from baseline in CSFT over the period Week 4 to Week 52 / 100 for the study eye |
|-----------------|-----------------------------------------------------------------------------------------------------|

**End point description:**

The thickness of the retina was measured using Spectral Domain (SD) optical coherence tomography (OCT) equipment (SD-OCT) and reported as a difference, in micrometers. a negative change from baseline indicates a reduction in thickness, whereas a positive change from baseline indicates an increase. An increase in thickness may indicate a progression of the underlying disease. CSFT assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

**End point timeframe:**

|                                                                         |
|-------------------------------------------------------------------------|
| Baseline, period Week 4 through Week 52, period Week 4 through Week 100 |
|-------------------------------------------------------------------------|

| End point values                             | Brolucizumab 6 mg         | Aflibercept 2 mg          |  |  |
|----------------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type                           | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed                  | 179                       | 181                       |  |  |
| Units: Micrometers                           |                           |                           |  |  |
| least squares mean (confidence interval 95%) |                           |                           |  |  |
| period Week 4 through Week 52                | -172.8 (-185.8 to -159.8) | -145.4 (-158.4 to -132.4) |  |  |
| period Week 4 through Week 100               | -181.8 (-194.7 to -168.9) | -156.1 (-169.0 to -143.2) |  |  |

**Statistical analyses**

| Statistical analysis title              | CSFT over period Week 4 through Week 52 |
|-----------------------------------------|-----------------------------------------|
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg    |
| Number of subjects included in analysis | 360                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | other <sup>[34]</sup>                   |
| Parameter estimate                      | LS mean difference                      |
| Point estimate                          | -27.4                                   |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -45.8                                   |
| upper limit                             | -9                                      |
| Variability estimate                    | Standard error of the mean              |
| Dispersion value                        | 9.35                                    |

**Notes:**

[34] - Treatment difference

| Statistical analysis title | CSFT over period Week 4 through Week 100 |
|----------------------------|------------------------------------------|
| Comparison groups          | Brolucizumab 6 mg v Aflibercept 2 mg     |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 360                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other <sup>[35]</sup>      |
| Parameter estimate                      | LS mean difference         |
| Point estimate                          | -25.8                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -44                        |
| upper limit                             | -7.5                       |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 9.29                       |

Notes:

[35] - Treatment difference

### Secondary: Percentage of participants with normal CSFT thickness (<280 micrometers) at each post-baseline visit for the study eye

|                 |                                                                                                                        |
|-----------------|------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants with normal CSFT thickness (<280 micrometers) at each post-baseline visit for the study eye |
|-----------------|------------------------------------------------------------------------------------------------------------------------|

End point description:

The thickness of the retina was measured using Spectral Domain (SD) optical coherence tomography (OCT) equipment (SD-OCT) and reported as a difference, in micrometers. CSFT assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 4                            | 12.8 (8.3 to 18.7)  | 13.3 (8.7 to 19.2)  |  |  |
| Week 6                            | 16.8 (11.6 to 23.1) | 14.4 (9.7 to 20.4)  |  |  |
| Week 8                            | 22.9 (17.0 to 29.8) | 16.7 (11.5 to 22.9) |  |  |
| Week 12                           | 30.2 (23.5 to 37.5) | 24.4 (18.4 to 31.4) |  |  |
| Week 16                           | 36.9 (29.8 to 44.4) | 29.4 (22.9 to 36.7) |  |  |
| Week 18                           | 39.1 (31.9 to 46.7) | 30.0 (23.4 to 37.3) |  |  |
| Week 20                           | 42.5 (35.1 to 50.1) | 31.1 (24.4 to 38.4) |  |  |
| Week 24                           | 48.6 (41.1 to 56.2) | 29.4 (22.9 to 36.7) |  |  |

|          |                     |                     |  |  |
|----------|---------------------|---------------------|--|--|
| Week 28  | 50.3 (42.7 to 57.8) | 33.9 (27.0 to 41.3) |  |  |
| Week 32  | 48.0 (40.5 to 55.6) | 30.6 (23.9 to 37.8) |  |  |
| Week 36  | 38.5 (31.4 to 46.1) | 38.9 (31.7 to 46.4) |  |  |
| Week 40  | 51.4 (43.8 to 58.9) | 37.2 (30.1 to 44.7) |  |  |
| Week 44  | 51.4 (43.8 to 58.9) | 38.9 (31.7 to 46.4) |  |  |
| Week 48  | 49.7 (42.2 to 57.3) | 37.2 (30.1 to 44.7) |  |  |
| Week 52  | 57.5 (49.9 to 64.9) | 41.4 (34.2 to 49.0) |  |  |
| Week 56  | 57.5 (49.9 to 64.9) | 40.3 (33.1 to 47.9) |  |  |
| Week 60  | 53.1 (45.5 to 60.6) | 40.3 (33.1 to 47.9) |  |  |
| Week 64  | 54.2 (46.6 to 61.6) | 38.1 (31.0 to 45.6) |  |  |
| Week 68  | 53.6 (46.0 to 61.1) | 41.4 (34.2 to 49.0) |  |  |
| Week 72  | 56.4 (48.8 to 63.8) | 38.7 (31.5 to 46.2) |  |  |
| Week 76  | 55.3 (47.7 to 62.7) | 42.5 (35.2 to 50.1) |  |  |
| Week 80  | 57.0 (49.4 to 64.3) | 39.8 (32.6 to 47.3) |  |  |
| Week 84  | 57.0 (49.4 to 64.3) | 43.1 (35.8 to 50.6) |  |  |
| Week 88  | 56.4 (48.8 to 63.8) | 41.4 (34.2 to 49.0) |  |  |
| Week 92  | 57.0 (49.4 to 64.3) | 45.9 (38.4 to 53.4) |  |  |
| Week 96  | 59.8 (52.2 to 67.0) | 43.6 (36.3 to 51.2) |  |  |
| Week 100 | 62.0 (54.5 to 69.1) | 47.0 (39.5 to 54.5) |  |  |

## Statistical analyses

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | CSFT thickness (<280 micrometers) at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg          |
| Number of subjects included in analysis | 360                                           |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | other <sup>[36]</sup>                         |
| Parameter estimate                      | Clopper-Pearson exact method                  |
| Point estimate                          | 14.7                                          |
| Confidence interval                     |                                               |
| level                                   | 95 %                                          |
| sides                                   | 2-sided                                       |
| lower limit                             | 4.2                                           |
| upper limit                             | 24.9                                          |

Notes:

[36] - Treatment difference

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | CSFT thickness (<280 micrometers) at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg         |
| Number of subjects included in analysis | 360                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           | other <sup>[37]</sup>                        |
| Parameter estimate                      | Clopper-Pearson exact method                 |
| Point estimate                          | 16.3                                         |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | 5.7                                          |
| upper limit                             | 25.9                                         |

Notes:

[37] - Treatment difference

### Secondary: Percentage of patients with presence of Subretinal Fluid (SRF) in the study eye at each post-baseline visit

|                 |                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of patients with presence of Subretinal Fluid (SRF) in the study eye at each post-baseline visit |
|-----------------|-------------------------------------------------------------------------------------------------------------|

End point description:

Presence of Subretinal Fluid (SRF) in the study eye was assessed by spectral domain optical coherence tomography (SD-OCT), angiography, and/or color fundus photography. Subretinal fluid status assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg  | Aflibercept 2 mg    |  |  |
|-----------------------------------|--------------------|---------------------|--|--|
| Subject group type                | Reporting group    | Reporting group     |  |  |
| Number of subjects analysed       | 179                | 181                 |  |  |
| Units: Percentage of Participants |                    |                     |  |  |
| number (confidence interval 95%)  |                    |                     |  |  |
| Week 4                            | 12.3 (7.9 to 18.0) | 19.3 (13.9 to 25.9) |  |  |
| Week 6                            | 10.1 (6.1 to 15.4) | 13.8 (9.1 to 19.7)  |  |  |
| Week 8                            | 5.6 (2.7 to 10.0)  | 12.2 (7.8 to 17.8)  |  |  |
| Week 12                           | 3.9 (1.6 to 7.9)   | 7.7 (4.3 to 12.6)   |  |  |
| Week 16                           | 1.7 (0.3 to 4.8)   | 3.9 (1.6 to 7.8)    |  |  |
| Week 18                           | 2.2 (0.6 to 5.6)   | 2.2 (0.6 to 5.6)    |  |  |
| Week 20                           | 1.7 (0.3 to 4.8)   | 3.3 (1.2 to 7.1)    |  |  |

|          |                   |                   |  |  |
|----------|-------------------|-------------------|--|--|
| Week 24  | 2.2 (0.6 to 5.6)  | 6.6 (3.5 to 11.3) |  |  |
| Week 28  | 2.2 (0.6 to 5.6)  | 2.8 (0.9 to 6.3)  |  |  |
| Week 32  | 5.0 (2.3 to 9.3)  | 3.9 (1.6 to 7.8)  |  |  |
| Week 36  | 6.7 (3.5 to 11.4) | 1.7 (0.3 to 4.8)  |  |  |
| Week 40  | 4.5 (1.9 to 8.6)  | 2.8 (0.9 to 6.3)  |  |  |
| Week 44  | 2.2 (0.6 to 5.6)  | 2.8 (0.9 to 6.3)  |  |  |
| Week 48  | 6.1 (3.1 to 10.7) | 5.0 (2.3 to 9.2)  |  |  |
| Week 52  | 1.7 (0.3 to 4.8)  | 3.3 (1.2 to 7.1)  |  |  |
| Week 56  | 2.8 (0.9 to 6.4)  | 2.2 (0.6 to 5.6)  |  |  |
| Week 60  | 2.8 (0.9 to 6.4)  | 2.2 (0.6 to 5.6)  |  |  |
| Week 64  | 2.2 (0.6 to 5.6)  | 3.9 (1.6 to 7.8)  |  |  |
| Week 68  | 3.4 (1.2 to 7.2)  | 4.4 (1.9 to 8.5)  |  |  |
| Week 72  | 3.4 (1.2 to 7.2)  | 2.8 (0.9 to 6.3)  |  |  |
| Week 76  | 3.9 (1.6 to 7.9)  | 2.2 (0.6 to 5.6)  |  |  |
| Week 80  | 4.5 (1.9 to 8.6)  | 2.2 (0.6 to 5.6)  |  |  |
| Week 84  | 2.2 (0.6 to 5.6)  | 2.2 (0.6 to 5.6)  |  |  |
| Week 88  | 3.4 (1.2 to 7.2)  | 2.2 (0.6 to 5.6)  |  |  |
| Week 92  | 1.7 (0.3 to 4.8)  | 1.1 (0.1 to 3.9)  |  |  |
| Week 96  | 2.2 (0.6 to 5.6)  | 2.8 (0.9 to 6.3)  |  |  |
| Week 100 | 2.2 (0.6 to 5.6)  | 2.8 (0.9 to 6.3)  |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Subretinal Fluid (SRF) at Week 52    |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other <sup>[38]</sup>                |
| Parameter estimate                      | Clopper-Pearson exact method         |
| Point estimate                          | -1.2                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -4.5                                 |
| upper limit                             | 2.1                                  |

Notes:

[38] - Treatment Difference

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Subretinal Fluid (SRF) at Week 100   |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other <sup>[39]</sup>                |
| Parameter estimate                      | Clopper-Pearson exact method         |
| Point estimate                          | -0.2                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -3.4    |
| upper limit         | 3.4     |

Notes:

[39] - Treatment Difference

### Secondary: Percentage of patients with presence of Intraretinal Fluid (IRF) in the study eye at each post-baseline visit

|                 |                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of patients with presence of Intraretinal Fluid (IRF) in the study eye at each post-baseline visit |
|-----------------|---------------------------------------------------------------------------------------------------------------|

End point description:

Presence of Intraretinal Fluid (IRF) in the study eye was assessed by spectral domain optical coherence tomography (SD-OCT), angiography, and/or color fundus photography. Intraretinal fluid status assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 4                            | 88.3 (82.6 to 92.6) | 89.0 (83.5 to 93.1) |  |  |
| Week 6                            | 85.5 (79.4 to 90.3) | 86.2 (80.3 to 90.9) |  |  |
| Week 8                            | 87.2 (81.3 to 91.7) | 84.5 (78.4 to 89.5) |  |  |
| Week 12                           | 83.8 (77.6 to 88.9) | 85.6 (79.7 to 90.4) |  |  |
| Week 16                           | 76.0 (69.0 to 82.0) | 84.0 (77.8 to 89.0) |  |  |
| Week 18                           | 77.7 (70.8 to 83.5) | 81.2 (74.8 to 86.6) |  |  |
| Week 20                           | 72.6 (65.5 to 79.0) | 79.6 (72.9 to 85.2) |  |  |
| Week 24                           | 69.8 (62.5 to 76.5) | 82.3 (76.0 to 87.6) |  |  |
| Week 28                           | 67.6 (60.2 to 74.4) | 75.1 (68.2 to 81.3) |  |  |
| Week 32                           | 67.6 (60.2 to 74.4) | 76.8 (70.0 to 82.7) |  |  |
| Week 36                           | 73.2 (66.1 to 79.5) | 72.4 (65.3 to 78.7) |  |  |
| Week 40                           | 57.5 (49.9 to 64.9) | 74.0 (67.0 to 80.3) |  |  |
| Week 44                           | 56.4 (48.8 to 63.8) | 71.3 (64.1 to 77.7) |  |  |

|          |                     |                     |  |  |
|----------|---------------------|---------------------|--|--|
| Week 48  | 60.9 (53.3 to 68.1) | 75.7 (68.8 to 81.7) |  |  |
| Week 52  | 53.6 (46.0 to 61.1) | 72.9 (65.8 to 79.3) |  |  |
| Week 56  | 51.4 (43.8 to 58.9) | 70.2 (62.9 to 76.7) |  |  |
| Week 60  | 55.3 (47.7 to 62.7) | 69.1 (61.8 to 75.7) |  |  |
| Week 64  | 48.6 (41.1 to 56.2) | 69.6 (62.4 to 76.2) |  |  |
| Week 68  | 47.5 (40.0 to 55.1) | 66.9 (59.5 to 73.7) |  |  |
| Week 72  | 45.8 (38.4 to 53.4) | 66.9 (59.5 to 73.7) |  |  |
| Week 76  | 50.3 (42.7 to 57.8) | 63.0 (55.5 to 70.0) |  |  |
| Week 80  | 45.8 (38.4 to 53.4) | 65.7 (58.3 to 72.6) |  |  |
| Week 84  | 40.2 (33.0 to 47.8) | 63.0 (55.5 to 70.0) |  |  |
| Week 88  | 48.0 (40.5 to 55.6) | 64.1 (56.6 to 71.1) |  |  |
| Week 92  | 44.7 (37.3 to 52.3) | 59.1 (51.6 to 66.4) |  |  |
| Week 96  | 41.3 (34.0 to 48.9) | 61.9 (54.4 to 69.0) |  |  |
| Week 100 | 40.8 (33.5 to 48.4) | 56.9 (49.4 to 64.2) |  |  |

### Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Intraretinal Fluid (IRF) at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other <sup>[40]</sup>                |
| Parameter estimate                      | Clopper-Pearson exact method         |
| Point estimate                          | -16.1                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -26.3                                |
| upper limit                             | -5.7                                 |

Notes:

[40] - Treatment Difference

|                                   |                                      |
|-----------------------------------|--------------------------------------|
| <b>Statistical analysis title</b> | Intraretinal Fluid (IRF) at Week 52  |
| Comparison groups                 | Brolucizumab 6 mg v Aflibercept 2 mg |

|                                         |                              |
|-----------------------------------------|------------------------------|
| Number of subjects included in analysis | 360                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other <sup>[41]</sup>        |
| Parameter estimate                      | Clopper-Pearson exact method |
| Point estimate                          | -19.1                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -28.9                        |
| upper limit                             | -9.2                         |

Notes:

[41] - Treatment Difference

### Secondary: Percentage of patients with presence of Subretinal Fluid (SRF) and/or Intraretinal Fluid (IRF) in the study eye at each post-baseline visit

|                 |                                                                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of patients with presence of Subretinal Fluid (SRF) and/or Intraretinal Fluid (IRF) in the study eye at each post-baseline visit |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Presence of Subretinal Fluid (SRF) and/or Intraretinal Fluid (IRF) in the study eye was assessed by spectral domain optical coherence tomography (SD-OCT), angiography, and/or color fundus photography. Fluid status (SRF and/or IRF) assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Week 4, Week 6, Week 8, Week 12, Week 16, Week 18, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 52, Week 56, Week 60, Week 64, Week 68, Week 72, Week 76, Week 80, Week 84, Week 88, Week 92, Week 96, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 4                            | 90.5 (85.2 to 94.4) | 90.6 (85.4 to 94.4) |  |  |
| Week 6                            | 86.6 (80.7 to 91.2) | 88.4 (82.8 to 92.7) |  |  |
| Week 8                            | 87.2 (81.3 to 91.7) | 85.6 (79.7 to 90.4) |  |  |
| Week 12                           | 83.8 (77.6 to 88.9) | 86.2 (80.3 to 90.9) |  |  |
| Week 16                           | 76.0 (69.0 to 82.0) | 84.0 (77.8 to 89.0) |  |  |
| Week 18                           | 78.2 (71.4 to 84.0) | 81.2 (74.8 to 86.6) |  |  |
| Week 20                           | 73.2 (66.1 to 79.5) | 79.6 (72.9 to 85.2) |  |  |
| Week 24                           | 70.4 (63.1 to 77.0) | 82.3 (76.0 to 87.6) |  |  |
| Week 28                           | 68.7 (61.4 to 75.4) | 75.1 (68.2 to 81.3) |  |  |

|          |                     |                     |  |  |
|----------|---------------------|---------------------|--|--|
| Week 32  | 68.7 (61.4 to 75.4) | 76.8 (70.0 to 82.7) |  |  |
| Week 36  | 73.7 (66.7 to 80.0) | 72.4 (65.3 to 78.7) |  |  |
| Week 40  | 58.1 (50.5 to 65.4) | 74.0 (67.0 to 80.3) |  |  |
| Week 44  | 57.0 (49.4 to 64.3) | 71.3 (64.1 to 77.7) |  |  |
| Week 48  | 61.5 (53.9 to 68.6) | 75.7 (68.8 to 81.7) |  |  |
| Week 52  | 54.2 (46.6 to 61.6) | 72.9 (65.8 to 79.3) |  |  |
| Week 56  | 52.0 (44.4 to 59.5) | 70.2 (62.9 to 76.7) |  |  |
| Week 60  | 55.3 (47.7 to 62.7) | 69.1 (61.8 to 75.7) |  |  |
| Week 64  | 49.2 (41.6 to 56.7) | 69.6 (62.4 to 76.2) |  |  |
| Week 68  | 48.0 (40.5 to 55.6) | 68.0 (60.6 to 74.7) |  |  |
| Week 72  | 46.9 (39.4 to 54.5) | 66.9 (59.5 to 73.7) |  |  |
| Week 76  | 50.8 (43.3 to 58.4) | 63.0 (55.5 to 70.0) |  |  |
| Week 80  | 46.4 (38.9 to 54.0) | 65.7 (58.3 to 72.6) |  |  |
| Week 84  | 40.8 (33.5 to 48.4) | 63.0 (55.5 to 70.0) |  |  |
| Week 88  | 48.6 (41.1 to 56.2) | 64.1 (56.6 to 71.1) |  |  |
| Week 92  | 45.3 (37.8 to 52.8) | 59.1 (51.6 to 66.4) |  |  |
| Week 96  | 41.3 (34.0 to 48.9) | 61.9 (54.4 to 69.0) |  |  |
| Week 100 | 40.8 (33.5 to 48.4) | 56.9 (49.4 to 64.2) |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | SRF and/or IRF at Week 52            |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other <sup>[42]</sup>                |
| Parameter estimate                      | Clopper-Pearson exact method         |
| Point estimate                          | -18.4                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -28.5                                |
| upper limit                             | -8.3                                 |

Notes:

[42] - Treatment Difference

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | SRF and/or IRF at Week 100 |
|-----------------------------------|----------------------------|

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other <sup>[43]</sup>                |
| Parameter estimate                      | Clopper-Pearson exact method         |
| Point estimate                          | -16.2                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -26.4                                |
| upper limit                             | -5.9                                 |

Notes:

[43] - Treatment difference

### Secondary: Percentage of participants with presence of leakage on Fluorescein Angiography (FA) at Weeks 52 and 100

|                 |                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants with presence of leakage on Fluorescein Angiography (FA) at Weeks 52 and 100 |
|-----------------|---------------------------------------------------------------------------------------------------------|

End point description:

Presence of leakage on Fluorescein Angiography as assessed by fluorescein angiography. Leakage on FA assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Week 52, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 52                           | 54.7 (47.2 to 62.2) | 79.4 (72.8 to 85.1) |  |  |
| Week 100                          | 46.9 (39.4 to 54.5) | 65.6 (58.1 to 72.5) |  |  |

### Statistical analyses

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| <b>Statistical analysis title</b>       | Fluorescein Angiography (FA) at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg     |
| Number of subjects included in analysis | 360                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other <sup>[44]</sup>                    |
| Parameter estimate                      | Clopper-Pearson exact method             |
| Point estimate                          | -19.1                                    |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -29.1   |
| upper limit         | -8.2    |

Notes:

[44] - Treatment difference

|                                         |                                         |
|-----------------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b>       | Fluorescein Angiography (FA) at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg    |
| Number of subjects included in analysis | 360                                     |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | other <sup>[45]</sup>                   |
| Parameter estimate                      | Clopper-Pearson exact method            |
| Point estimate                          | -25.4                                   |
| Confidence interval                     |                                         |
| level                                   | 95 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -34.4                                   |
| upper limit                             | -16.3                                   |

Notes:

[45] - Treatment difference

### Secondary: Percentage of Participants with with $\geq 2$ -step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

|                 |                                                                                                                                               |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with with $\geq 2$ -step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The Diabetic Retinopathy Disease Severity Scale measures the 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                  | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 28                           | 25.0 (18.8 to 32.1) | 20.9 (15.2 to 27.6) |  |  |
| Week 52                           | 29.0 (22.4 to 36.3) | 27.7 (21.2 to 34.9) |  |  |
| Week 76                           | 30.1 (23.4 to 37.5) | 30.5 (23.8 to 37.9) |  |  |
| Week 100                          | 35.8 (28.7 to 43.4) | 31.1 (24.3 to 38.5) |  |  |

## Statistical analyses

|                                         |                                                          |
|-----------------------------------------|----------------------------------------------------------|
| <b>Statistical analysis title</b>       | <b>&gt;=2-step improvement in ETDRS-DRSS at Week 100</b> |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg                     |
| Number of subjects included in analysis | 360                                                      |
| Analysis specification                  | Pre-specified                                            |
| Analysis type                           | other <sup>[46]</sup>                                    |
| Parameter estimate                      | Clopper-Pearson exact method                             |
| Point estimate                          | 4.5                                                      |
| Confidence interval                     |                                                          |
| level                                   | 95 %                                                     |
| sides                                   | 2-sided                                                  |
| lower limit                             | -1.7                                                     |
| upper limit                             | 10.8                                                     |

Notes:

[46] - Treatment difference

|                                         |                                                         |
|-----------------------------------------|---------------------------------------------------------|
| <b>Statistical analysis title</b>       | <b>&gt;=2-step improvement in ETDRS-DRSS at Week 52</b> |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg                    |
| Number of subjects included in analysis | 360                                                     |
| Analysis specification                  | Pre-specified                                           |
| Analysis type                           | other <sup>[47]</sup>                                   |
| Parameter estimate                      | Clopper-Pearson exact method                            |
| Point estimate                          | 1.1                                                     |
| Confidence interval                     |                                                         |
| level                                   | 95 %                                                    |
| sides                                   | 2-sided                                                 |
| lower limit                             | -5.6                                                    |
| upper limit                             | 7.8                                                     |

Notes:

[47] - Treatment difference

## Secondary: Percentage of Participants with with >=3-step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

|                 |                                                                                                                                         |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with with >=3-step improvement from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The Diabetic Retinopathy Disease Severity Scale measures the 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| <b>End point values</b>           | Brolucizumab 6 mg   | Aflibercept 2 mg    |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 179                 | 181                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  |                     |                     |  |  |
| Week 28                           | 13.1 (8.5 to 19.0)  | 11.3 (7.0 to 16.9)  |  |  |
| Week 52                           | 14.8 (9.9 to 20.9)  | 15.3 (10.3 to 21.4) |  |  |
| Week 76                           | 18.8 (13.3 to 25.3) | 15.3 (10.3 to 21.4) |  |  |
| Week 100                          | 21.0 (15.3 to 27.8) | 16.9 (11.7 to 23.3) |  |  |

### Statistical analyses

|                                         |                                                |
|-----------------------------------------|------------------------------------------------|
| <b>Statistical analysis title</b>       | >=3-step improvement in ETDRS-DRSS at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg           |
| Number of subjects included in analysis | 360                                            |
| Analysis specification                  | Pre-specified                                  |
| Analysis type                           | other <sup>[48]</sup>                          |
| Parameter estimate                      | Clopper-Pearson exact method                   |
| Point estimate                          | 3.9                                            |
| Confidence interval                     |                                                |
| level                                   | 95 %                                           |
| sides                                   | 2-sided                                        |
| lower limit                             | -2.3                                           |
| upper limit                             | 10                                             |

Notes:

[48] - Treatment difference

|                                         |                                               |
|-----------------------------------------|-----------------------------------------------|
| <b>Statistical analysis title</b>       | >=3-step improvement in ETDRS-DRSS at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg          |
| Number of subjects included in analysis | 360                                           |
| Analysis specification                  | Pre-specified                                 |
| Analysis type                           | other <sup>[49]</sup>                         |
| Parameter estimate                      | Clopper-Pearson exact method                  |
| Point estimate                          | -0.6                                          |
| Confidence interval                     |                                               |
| level                                   | 95 %                                          |
| sides                                   | 2-sided                                       |
| lower limit                             | -7.1                                          |
| upper limit                             | 5.7                                           |

Notes:

[49] - Treatment difference

### Secondary: Percentage of Participants with with $\geq 2$ -step worsening from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

|                 |                                                                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with with $\geq 2$ -step worsening from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The Diabetic Retinopathy Disease Severity Scale was based on 7-field stereo color fundus photography and measured 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                  | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------------|-------------------|------------------|--|--|
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 179               | 181              |  |  |
| Units: Percentage of Participants |                   |                  |  |  |
| number (confidence interval 95%)  |                   |                  |  |  |
| Week 28                           | 2.3 (0.6 to 5.7)  | 0.6 (0.0 to 3.1) |  |  |
| Week 52                           | 1.7 (0.4 to 4.9)  | 0.6 (0.0 to 3.1) |  |  |
| Week 76                           | 3.4 (1.3 to 7.3)  | 0.6 (0.0 to 3.1) |  |  |
| Week 100                          | 4.5 (2.0 to 8.8)  | 1.7 (0.4 to 4.9) |  |  |

### Statistical analyses

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| Statistical analysis title              | $\geq 2$ -step worsening in ETDRS-DRSS at Week 100 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg               |
| Number of subjects included in analysis | 360                                                |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | other <sup>[50]</sup>                              |
| Parameter estimate                      | Clopper-Pearson exact method                       |
| Point estimate                          | 2.9                                                |
| Confidence interval                     |                                                    |
| level                                   | 95 %                                               |
| sides                                   | 2-sided                                            |
| lower limit                             | -0.5                                               |
| upper limit                             | 6.9                                                |

Notes:

[50] - Treatment difference

|                            |                                                   |
|----------------------------|---------------------------------------------------|
| Statistical analysis title | $\geq 2$ -step worsening in ETDRS-DRSS at Week 52 |
| Comparison groups          | Brolucizumab 6 mg v Aflibercept 2 mg              |

|                                         |                              |
|-----------------------------------------|------------------------------|
| Number of subjects included in analysis | 360                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other <sup>[51]</sup>        |
| Parameter estimate                      | Clopper-Pearson exact method |
| Point estimate                          | 1.1                          |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -1                           |
| upper limit                             | 3.6                          |

Notes:

[51] - Treatment difference

### Secondary: Percentage of Participants with with $\geq 3$ -step worsening from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score

|                 |                                                                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with with $\geq 3$ -step worsening from Baseline in ETDRS Diabetic Retinopathy Severity Scale (ETDRS-DRSS) score |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The Diabetic Retinopathy Disease Severity Scale was based on 7-field stereo color fundus photography and measured 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                  | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------------|-------------------|------------------|--|--|
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 179               | 181              |  |  |
| Units: Percentage of Participants |                   |                  |  |  |
| number (confidence interval 95%)  |                   |                  |  |  |
| Week 28                           | 0.6 (0.0 to 3.1)  | 999 (999 to 999) |  |  |
| Week 52                           | 0.6 (0.0 to 3.1)  | 999 (999 to 999) |  |  |
| Week 76                           | 0.6 (0.0 to 3.1)  | 999 (999 to 999) |  |  |
| Week 100                          | 0.6 (0.0 to 3.1)  | 1.1 (0.1 to 4.0) |  |  |

### Statistical analyses

|                            |                                                    |
|----------------------------|----------------------------------------------------|
| Statistical analysis title | $\geq 3$ -step worsening in ETDRS-DRSS at Week 100 |
| Comparison groups          | Brolucizumab 6 mg v Aflibercept 2 mg               |

|                                         |                              |
|-----------------------------------------|------------------------------|
| Number of subjects included in analysis | 360                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | other <sup>[52]</sup>        |
| Parameter estimate                      | Clopper-Pearson exact method |
| Point estimate                          | -0.6                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | -2.6                         |
| upper limit                             | 1.3                          |

Notes:

[52] - Treatment difference

|                                         |                                             |
|-----------------------------------------|---------------------------------------------|
| Statistical analysis title              | >=3-step worsening in ETDRS-DRSS at Week 52 |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg        |
| Number of subjects included in analysis | 360                                         |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | other <sup>[53]</sup>                       |
| Parameter estimate                      | Clopper-Pearson exact method                |
| Point estimate                          | 0.6                                         |
| Confidence interval                     |                                             |
| level                                   | 95 %                                        |
| sides                                   | 2-sided                                     |
| lower limit                             | 0.5                                         |
| upper limit                             | 2.1                                         |

Notes:

[53] - Treatment difference

### Secondary: Percentage of participants with progression to proliferative diabetic retinopathy (PDR) as assessed by ETDRS-DRSS Score of at least 61 by Week 100

|                 |                                                                                                                                                    |  |  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| End point title | Percentage of participants with progression to proliferative diabetic retinopathy (PDR) as assessed by ETDRS-DRSS Score of at least 61 by Week 100 |  |  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------|--|--|

End point description:

The Diabetic Retinopathy Disease Severity Scale was based on 7-field stereo color fundus photography and measured 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative. DRSS assessments after start of alternative diabetic macular edema (DME) treatment in the study eye were censored and replaced by the last value prior to start of this alternative treatment.

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

End point timeframe:

Week 100

|                                   |                   |                  |  |  |
|-----------------------------------|-------------------|------------------|--|--|
| <b>End point values</b>           | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
| Subject group type                | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed       | 179               | 181              |  |  |
| Units: Percentage of Participants |                   |                  |  |  |
| number (confidence interval 95%)  | 0.6 (0.0 to 3.4)  | 0.6 (0.0 to 3.4) |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | PDR of at least 61 by Week 100       |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 360                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | other <sup>[54]</sup>                |
| Parameter estimate                      | Clopper-Pearson exact method         |
| Point estimate                          | 0                                    |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -2.1                                 |
| upper limit                             | 1.9                                  |

Notes:

[54] - Treatment difference

## Secondary: Number of Participants with Ocular and Non-ocular Adverse Events (AEs)

|                 |                                                                        |
|-----------------|------------------------------------------------------------------------|
| End point title | Number of Participants with Ocular and Non-ocular Adverse Events (AEs) |
|-----------------|------------------------------------------------------------------------|

End point description:

The number of participants with ocular and non-ocular adverse events was assessed by CTCAE and reported categorically: Mild, Moderate, Severe.

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

End point timeframe:

From randomization till 30 days safety follow-up, assessed up to 35 months.

| <b>End point values</b>            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|------------------------------------|-------------------|------------------|--|--|
| Subject group type                 | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed        | 179               | 181              |  |  |
| Units: Participants                |                   |                  |  |  |
| Ocular adverse events Mild         | 52                | 47               |  |  |
| Non-ocular adverse events Mild     | 52                | 51               |  |  |
| Ocular adverse events Moderate     | 15                | 23               |  |  |
| Non-ocular adverse events Moderate | 51                | 50               |  |  |
| Ocular adverse events Severe       | 6                 | 4                |  |  |
| Non-ocular adverse events Severe   | 33                | 40               |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): composite score

|                 |                                                                                                                   |
|-----------------|-------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): composite score |
|-----------------|-------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 5.7 (± 11.91)     | 6.3 (± 10.19)    |  |  |
| Week 52                              | 8.9 (± 11.67)     | 6.7 (± 12.12)    |  |  |
| Week 76                              | 9.8 (± 12.22)     | 7.6 (± 11.81)    |  |  |
| Week 100                             | 9.0 (± 12.94)     | 6.2 (± 14.13)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - General Vision

|                 |                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - General Vision |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 9.0 (± 16.11)     | 10.2 (± 15.63)   |  |  |
| Week 52                              | 11.2 (± 17.05)    | 10.5 (± 17.14)   |  |  |
| Week 76                              | 12.4 (± 16.49)    | 12.0 (± 16.40)   |  |  |
| Week 100                             | 12.0 (± 16.25)    | 10.1 (± 18.73)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Ocular Pain

|                 |                                                                                                                                |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Ocular Pain |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 4.1 (± 19.52)     | 4.6 (± 18.48)    |  |  |
| Week 52                              | 4.6 (± 18.75)     | 4.4 (± 17.92)    |  |  |
| Week 76                              | 6.2 (± 16.95)     | 4.6 (± 18.68)    |  |  |
| Week 100                             | 4.3 (± 16.60)     | 5.4 (± 20.77)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Near Activities

|                 |                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Near Activities |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 6.4 (± 20.83)     | 6.3 (± 18.42)    |  |  |
| Week 52                              | 10.5 (± 20.30)    | 9.3 (± 19.57)    |  |  |
| Week 76                              | 11.0 (± 21.91)    | 9.2 (± 18.76)    |  |  |
| Week 100                             | 13.0 (± 20.21)    | 7.3 (± 21.71)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Distance Activities

|                 |                                                                                                                                        |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Distance Activities |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 6.2 (± 18.87)     | 5.6 (± 15.78)    |  |  |
| Week 52                              | 11.7 (± 17.62)    | 8.2 (± 17.12)    |  |  |
| Week 76                              | 12.1 (± 18.32)    | 8.1 (± 16.71)    |  |  |
| Week 100                             | 11.4 (± 18.94)    | 6.6 (± 19.07)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Social Functioning

|                 |                                                                                                                                       |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Social Functioning |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 3.3 (± 15.82)     | 4.4 (± 16.48)    |  |  |
| Week 52                              | 7.1 (± 16.22)     | 4.9 (± 15.59)    |  |  |
| Week 76                              | 6.3 (± 16.65)     | 5.0 (± 15.34)    |  |  |
| Week 100                             | 6.1 (± 16.78)     | 4.1 (± 17.55)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Mental Health

|                 |                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Mental Health |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 7.9 (± 19.53)     | 10.1 (± 19.90)   |  |  |
| Week 52                              | 12.6 (± 22.42)    | 10.1 (± 22.78)   |  |  |
| Week 76                              | 13.5 (± 21.02)    | 13.1 (± 23.10)   |  |  |
| Week 100                             | 13.3 (± 20.91)    | 11.6 (± 26.31)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Role Difficulties

|                 |                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Role Difficulties |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 6.9 (± 25.13)     | 9.4 (± 23.41)    |  |  |
| Week 52                              | 12.2 (± 24.76)    | 8.7 (± 27.21)    |  |  |
| Week 76                              | 14.0 (± 28.44)    | 11.4 (± 27.83)   |  |  |
| Week 100                             | 12.3 (± 28.14)    | 10.2 (± 27.12)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Dependency

|                 |                                                                                                                               |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Dependency |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 5.5 (± 19.39)     | 3.6 (± 20.34)    |  |  |
| Week 52                              | 7.6 (± 19.53)     | 3.9 (± 22.49)    |  |  |
| Week 76                              | 7.3 (± 20.19)     | 5.6 (± 23.24)    |  |  |
| Week 100                             | 6.8 (± 19.85)     | 2.9 (± 24.79)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Driving

|                 |                                                                                                                            |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Driving |
|-----------------|----------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 1.4 (± 18.75)     | 4.8 (± 12.24)    |  |  |
| Week 52                              | 6.4 (± 14.63)     | 4.2 (± 12.81)    |  |  |
| Week 76                              | 8.9 (± 15.95)     | 2.8 (± 15.88)    |  |  |
| Week 100                             | 5.4 (± 15.81)     | 1.2 (± 16.75)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Color Vision

|                 |                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Color Vision |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 3.5 (± 15.10)     | 4.2 (± 12.50)    |  |  |
| Week 52                              | 5.8 (± 15.08)     | 3.6 (± 13.09)    |  |  |
| Week 76                              | 5.2 (± 15.73)     | 3.9 (± 13.79)    |  |  |
| Week 100                             | 4.3 (± 14.70)     | 3.2 (± 15.48)    |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Peripheral Vision

|                 |                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): subscale score - Peripheral Vision |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 5.3 (± 18.83)     | 4.0 (± 16.99)    |  |  |
| Week 52                              | 7.2 (± 18.68)     | 3.2 (± 19.77)    |  |  |
| Week 76                              | 9.3 (± 19.64)     | 4.3 (± 17.82)    |  |  |
| Week 100                             | 8.5 (± 19.33)     | 2.3 (± 19.37)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): General Health Rating

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Change from Baseline in the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25): General Health Rating |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

End point description:

The survey consisted of 25 items representing 11 vision related constructs (general vision, ocular pain, near activities, distance activities, social functioning, mental health, role difficulties, dependency, driving, color vision, peripheral vision) plus a single-item general health rating question. The score of each individual question ranged from 0 (worst) to 100 which indicated the best possible response. The composite score and score of each construct also ranged from 0 to 100 as they were calculated as total scores divided by the number of questions. The higher the values of total scores represented better outcome.

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

End point timeframe:

Baseline, Week 28, Week 52, Week 76, Week 100

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------|-------------------|------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed          | 179               | 181              |  |  |
| Units: Score on a scale              |                   |                  |  |  |
| arithmetic mean (standard deviation) |                   |                  |  |  |
| Week 28                              | 3.9 (± 18.66)     | 4.3 (± 19.92)    |  |  |
| Week 52                              | 5.8 (± 22.34)     | 4.8 (± 23.12)    |  |  |
| Week 76                              | 8.9 (± 21.21)     | 7.1 (± 22.57)    |  |  |
| Week 100                             | 6.7 (± 19.14)     | 5.7 (± 21.80)    |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Systemic brolucizumab concentration

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | Systemic brolucizumab concentration |
|-----------------|-------------------------------------|

End point description:

Serum samples were taken approximately 24 hours after the first dose and 24 hours after the treatment at Week 24 to confirm the systemic brolucizumab exposure in patients with visual impairment due to diabetic macular edema.

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

End point timeframe:

Up to Week 24

| End point values                     | Brolucizumab 6 mg | Aflibercept 2 mg  |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 179               | 0 <sup>[55]</sup> |  |  |
| Units: ng/mL                         |                   |                   |  |  |
| arithmetic mean (standard deviation) |                   |                   |  |  |
| Day 2                                | 56.2 (± 10.4)     | ( )               |  |  |
| Week 4                               | 0.760 (± 1.98)    | ( )               |  |  |
| Week 12                              | 999 (± 999)       | ( )               |  |  |
| Week 24                              | 999 (± 999)       | ( )               |  |  |
| Week 24 + 1 Day                      | 41.5 (± 80.5)     | ( )               |  |  |

Notes:

[55] - Endpoint applicable to Brolucizumab treatment arm only

## Statistical analyses

No statistical analyses for this end point

## Secondary: Distribution of integrated Anti-Drug Antibody (ADA) status in the brolucizumab arm

|                                                                                                                                                                                                                                          |                                                                                    |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                          | Distribution of integrated Anti-Drug Antibody (ADA) status in the brolucizumab arm |
| End point description:                                                                                                                                                                                                                   |                                                                                    |
| Integrated ADA Status was categorized: ADA negative or ADA positive with no boost, Induced or Boosted, Missing ADA at pre-dose or no post-dose ADA data.                                                                                 |                                                                                    |
| - ADA negative: (a) ADA negative at all time points (pre-dose and post-dose), (b) ADA negative at pre-dose and no titer values above 40 at all other time points, (c) ADA titer of 40 at pre-dose but negative at all other time points. |                                                                                    |
| - ADA positive with no boost: ADA positive at pre-dose, post-dose titer values do not increase from pre-dose by more than 3-fold (1 dilution) at any time point.                                                                         |                                                                                    |
| - Induced: ADA negative at pre-dose, post-dose titer value of 120 or more at any time point.                                                                                                                                             |                                                                                    |
| - Boosted: ADA positive at pre-dose, post-dose titer values increase from pre-dose by more than 3-fold (1 dilution) at any time point.                                                                                                   |                                                                                    |
| End point type                                                                                                                                                                                                                           | Secondary                                                                          |
| End point timeframe:                                                                                                                                                                                                                     |                                                                                    |
| Up to Week 100                                                                                                                                                                                                                           |                                                                                    |

| End point values                                 | Brolucizumab 6 mg | Aflibercept 2 mg  |  |  |
|--------------------------------------------------|-------------------|-------------------|--|--|
| Subject group type                               | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed                      | 179               | 0 <sup>[56]</sup> |  |  |
| Units: Participants                              |                   |                   |  |  |
| ADA negative or ADA positive with no boost       | 146               |                   |  |  |
| Induced or Boosted                               | 27                |                   |  |  |
| Missing ADA at pre-dose or no post-dose ADA data | 6                 |                   |  |  |

Notes:

[56] - Endpoint applicable to Brolucizumab treatment arm only

## Statistical analyses

No statistical analyses for this end point

### Secondary: Distribution of integrated Anti-Drug Antibody (ADA) status in the brolucizumab arm - adjusted for pre-existing ADA status

|                 |                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Distribution of integrated Anti-Drug Antibody (ADA) status in the brolucizumab arm - adjusted for pre-existing ADA status |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|

End point description:

Integrated ADA Status - adjusted for pre-existing ADA status was categorized: ADA negative, ADA positive with no boost, Induced, Boosted.

- ADA negative: (a) ADA negative at all time points (pre-dose and post-dose), (b) ADA negative at pre-dose and no titer values above 40 at all other time points, (c) ADA titer of 40 at pre-dose but negative at all other time points.

- ADA positive with no boost: ADA positive at pre-dose, post-dose titer values do not increase from pre-dose by more than 3-fold (1 dilution) at any time point.

- Induced: ADA negative at pre-dose, post-dose titer value of 120 or more at any time point.

- Boosted: ADA positive at pre-dose, post-dose titer values increase from pre-dose by more than 3-fold (1 dilution) at any time point.

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

End point timeframe:

Up to Week 100

| End point values                                  | Brolucizumab 6 mg | Aflibercept 2 mg  |  |  |
|---------------------------------------------------|-------------------|-------------------|--|--|
| Subject group type                                | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed                       | 179               | 0 <sup>[57]</sup> |  |  |
| Units: Participants                               |                   |                   |  |  |
| ADA Negative and/or titer value of 40 at pre-dose | 53                |                   |  |  |
| ADA positive with no boost and/or at pre-dose     | 93                |                   |  |  |
| Induced/ADA Negative at pre-dose                  | 14                |                   |  |  |
| Boosted/ADA Positive at pre-dose                  | 13                |                   |  |  |

Notes:

[57] - Endpoint applicable to Brolucizumab treatment arm only

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pre-existing ADA status and incidence of Adverse Event of Special Interest (AESI) in the study eye

|                 |                                                                                                    |
|-----------------|----------------------------------------------------------------------------------------------------|
| End point title | Pre-existing ADA status and incidence of Adverse Event of Special Interest (AESI) in the study eye |
|-----------------|----------------------------------------------------------------------------------------------------|

End point description:

Pre-existing ADA status and incidence of Adverse Event of Special Interest (AESI) in the study eye was categorized: Negative, Positive.

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

End point timeframe:

Up to Week 100

| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg  |  |  |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type          | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed | 179               | 0 <sup>[58]</sup> |  |  |
| Units: Participants         |                   |                   |  |  |
| Negative At least 1 AESI    | 1                 |                   |  |  |
| Positive At least 1 AESI    | 5                 |                   |  |  |
| Negative No AESI            | 63                |                   |  |  |
| Positive No AESI            | 105               |                   |  |  |

Notes:

[58] - Endpoint applicable to Brolucizumab treatment arm only

### Statistical analyses

No statistical analyses for this end point

### Secondary: Integrated ADA status up to Week 100 and incidence of Adverse Event of Special Interest (AESI) in the study eye.

|                 |                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| End point title | Integrated ADA status up to Week 100 and incidence of Adverse Event of Special Interest (AESI) in the study eye. |
|-----------------|------------------------------------------------------------------------------------------------------------------|

End point description:

Integrated ADA status up to Week 100 and incidence of Adverse Event of Special Interest (AESI) in the study eye was categorized: ADA-negative or no boost, Induced or boosted.

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

End point timeframe:

Up to Week 100

| End point values                         | Brolucizumab 6 mg | Aflibercept 2 mg  |  |  |
|------------------------------------------|-------------------|-------------------|--|--|
| Subject group type                       | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed              | 179               | 0 <sup>[59]</sup> |  |  |
| Units: Participants                      |                   |                   |  |  |
| ADA-negative or no boost At least 1 AESI | 4                 |                   |  |  |
| Induced or boosted At least 1 AESI       | 2                 |                   |  |  |
| ADA-negative or no boost No AESI         | 142               |                   |  |  |
| Induced or boosted No AESI               | 25                |                   |  |  |

Notes:

[59] - Endpoint applicable to Brolucizumab treatment arm only

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment up to 30 days after last dose (maximum 35 months)

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Brolucizumab 6mg |
|-----------------------|------------------|

Reporting group description:

Brolucizumab 6mg

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

Reporting group description:

Overall

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Aflibercept 2mg |
|-----------------------|-----------------|

Reporting group description:

Aflibercept 2mg

| Serious adverse events                                              | Brolucizumab 6mg  | Overall            | Aflibercept 2mg   |
|---------------------------------------------------------------------|-------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                    |                   |
| subjects affected / exposed                                         | 53 / 179 (29.61%) | 113 / 360 (31.39%) | 60 / 181 (33.15%) |
| number of deaths (all causes)                                       | 13                | 22                 | 9                 |
| number of deaths resulting from adverse events                      | 0                 | 0                  | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                    |                   |
| Benign oesophageal neoplasm                                         |                   |                    |                   |
| subjects affected / exposed                                         | 1 / 179 (0.56%)   | 1 / 360 (0.28%)    | 0 / 181 (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             |
| Biliary neoplasm                                                    |                   |                    |                   |
| subjects affected / exposed                                         | 1 / 179 (0.56%)   | 1 / 360 (0.28%)    | 0 / 181 (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             |
| Bronchial carcinoma                                                 |                   |                    |                   |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Cholangiocarcinoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Colon adenoma                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colon cancer stage I                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Hepatic cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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 malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Malignant neoplasm of unknown primary site      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastasis                                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Neoplasm malignant                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ovarian cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Pleomorphic adenoma                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Squamous cell carcinoma of lung                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Waldenstrom's macroglobulinaemia                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Aortic stenosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Arterial stenosis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Arteriovenous fistula                           |                 |                 |                 |

|                                                      |                 |                 |                 |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Extremity necrosis                                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension                                         |                 |                 |                 |
| subjects affected / exposed                          | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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 arterial occlusive disease                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral ischaemia                                 |                 |                 |                 |
| subjects affected / exposed                          | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| General disorders and administration site conditions |                 |                 |                 |
| Death                                                |                 |                 |                 |
| subjects affected / exposed                          | 1 / 179 (0.56%) | 3 / 360 (0.83%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 3           | 0 / 2           |
| Mass                                                 |                 |                 |                 |
| subjects affected / exposed                          | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Oedema peripheral                                    |                 |                 |                 |
| subjects affected / exposed                          | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Sudden death                                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Immune system disorders                         |                 |                 |                 |
| Anaphylactic reaction                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Breast hypoplasia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Postmenopausal haemorrhage                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Asthma                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspnoea                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoventilation                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Pulmonary embolism                              |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary oedema                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Sleep apnoea syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Psychiatric disorders                           |                 |                 |                 |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Haemoglobin decreased                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fracture                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 179 (1.12%) | 2 / 360 (0.56%) | 0 / 181 (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           |
| Aortic valve stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Cardiac arrest                                  |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 2           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 179 (1.12%) | 6 / 360 (1.67%) | 4 / 181 (2.21%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 10          | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure acute                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Cardiogenic shock                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Cardiopulmonary failure                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 3 / 360 (0.83%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 2 / 179 (1.12%) | 3 / 360 (0.83%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 179 (0.00%) | 3 / 360 (0.83%) | 3 / 181 (1.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Nervous system disorders                        |                 |                 |                 |
| Arachnoiditis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bickerstaff's encephalitis                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Carotid artery stenosis                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Cerebellar haemorrhage                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebellar stroke                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 2 / 179 (1.12%) | 4 / 360 (1.11%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 4           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Haemorrhagic stroke                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Headache                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hemiparesis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Hypoglycaemic coma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Iron deficiency anaemia                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Microcytic anaemia                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo positional                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Glaucoma - Study eye                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal artery occlusion - Study eye            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Retinal detachment - Study eye                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal tear - Study eye                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Uveitis - Fellow eye                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Uveitis - Study eye                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vitreous haemorrhage - Fellow eye               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain upper                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenal ulcer                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspepsia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis acute                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal haemorrhage                              |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 179 (1.12%) | 2 / 360 (0.56%) | 0 / 181 (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           |
| <b>Hepatobiliary disorders</b>                  |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis chronic                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| 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>Skin and subcutaneous tissue disorders</b>   |                 |                 |                 |
| Diabetic foot                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| 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>Renal and urinary disorders</b>              |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Chronic kidney disease                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 3 / 360 (0.83%) | 3 / 181 (1.66%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic nephropathy                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 3 / 360 (0.83%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Dysuria                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephropathy                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Nephrotic syndrome                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocrine disorders                             |                 |                 |                 |
| Goitre                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Osteonecrosis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Bone abscess                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19                                        |                 |                 |                 |
| subjects affected / exposed                     | 4 / 179 (2.23%) | 7 / 360 (1.94%) | 3 / 181 (1.66%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 7           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 2           | 0 / 0           |
| COVID-19 pneumonia                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clostridium difficile colitis                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Endophthalmitis - Study eye                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 179 (1.12%) | 3 / 360 (0.83%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fungal oesophagitis                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gangrene                                        |                 |                 |                 |
| subjects affected / exposed                     | 3 / 179 (1.68%) | 5 / 360 (1.39%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 7           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Localised infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ophthalmic herpes zoster - Study eye            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Orchitis                                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Osteomyelitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 4 / 179 (2.23%) | 7 / 360 (1.94%) | 3 / 181 (1.66%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 7           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Pneumonia viral                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Streptococcal infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Diabetes mellitus inadequate control            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Fluid overload                                  |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |
| Fluid retention                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 2 / 360 (0.56%) | 2 / 181 (1.10%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gout                                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 1 / 360 (0.28%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 2 / 360 (0.56%) | 1 / 181 (0.55%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Type 1 diabetes mellitus                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 179 (0.56%) | 1 / 360 (0.28%) | 0 / 181 (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           |

Frequency threshold for reporting non-serious adverse events: 2 %

| <b>Non-serious adverse events</b>                     | Brolucizumab 6mg   | Overall            | Aflibercept 2mg    |
|-------------------------------------------------------|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                    |                    |
| subjects affected / exposed                           | 131 / 179 (73.18%) | 265 / 360 (73.61%) | 134 / 181 (74.03%) |
| Vascular disorders                                    |                    |                    |                    |
| Hypertension                                          |                    |                    |                    |
| subjects affected / exposed                           | 15 / 179 (8.38%)   | 32 / 360 (8.89%)   | 17 / 181 (9.39%)   |
| occurrences (all)                                     | 18                 | 41                 | 23                 |
| Peripheral arterial occlusive disease                 |                    |                    |                    |
| subjects affected / exposed                           | 4 / 179 (2.23%)    | 6 / 360 (1.67%)    | 2 / 181 (1.10%)    |
| occurrences (all)                                     | 4                  | 6                  | 2                  |
| General disorders and administration site conditions  |                    |                    |                    |

|                                                                                                                              |                       |                        |                        |
|------------------------------------------------------------------------------------------------------------------------------|-----------------------|------------------------|------------------------|
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                                                                 | 3 / 179 (1.68%)<br>3  | 10 / 360 (2.78%)<br>10 | 7 / 181 (3.87%)<br>7   |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                                                               | 4 / 179 (2.23%)<br>5  | 5 / 360 (1.39%)<br>6   | 1 / 181 (0.55%)<br>1   |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)                                                      | 0 / 179 (0.00%)<br>0  | 4 / 360 (1.11%)<br>4   | 4 / 181 (2.21%)<br>4   |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)                                                        | 4 / 179 (2.23%)<br>4  | 6 / 360 (1.67%)<br>6   | 2 / 181 (1.10%)<br>2   |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                                                                  | 8 / 179 (4.47%)<br>10 | 13 / 360 (3.61%)<br>15 | 5 / 181 (2.76%)<br>5   |
| Reproductive system and breast disorders<br>Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences (all) | 4 / 179 (2.23%)<br>4  | 7 / 360 (1.94%)<br>7   | 3 / 181 (1.66%)<br>3   |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)                 | 5 / 179 (2.79%)<br>5  | 15 / 360 (4.17%)<br>16 | 10 / 181 (5.52%)<br>11 |
| Investigations<br>Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                             | 8 / 179 (4.47%)<br>8  | 10 / 360 (2.78%)<br>10 | 2 / 181 (1.10%)<br>2   |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)                                                 | 5 / 179 (2.79%)<br>5  | 9 / 360 (2.50%)<br>9   | 4 / 181 (2.21%)<br>4   |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)                                            | 2 / 179 (1.12%)<br>2  | 8 / 360 (2.22%)<br>8   | 6 / 181 (3.31%)<br>6   |
| Blood urea increased<br>subjects affected / exposed<br>occurrences (all)                                                     | 3 / 179 (1.68%)<br>3  | 7 / 360 (1.94%)<br>7   | 4 / 181 (2.21%)<br>4   |

|                                                                                                    |                        |                        |                        |
|----------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| Glycosylated haemoglobin increased<br>subjects affected / exposed<br>occurrences (all)             | 7 / 179 (3.91%)<br>7   | 12 / 360 (3.33%)<br>12 | 5 / 181 (2.76%)<br>5   |
| Intraocular pressure increased -<br>Fellow eye<br>subjects affected / exposed<br>occurrences (all) | 2 / 179 (1.12%)<br>2   | 7 / 360 (1.94%)<br>8   | 5 / 181 (2.76%)<br>6   |
| Intraocular pressure increased -<br>Study eye<br>subjects affected / exposed<br>occurrences (all)  | 6 / 179 (3.35%)<br>8   | 10 / 360 (2.78%)<br>13 | 4 / 181 (2.21%)<br>5   |
| Protein urine present<br>subjects affected / exposed<br>occurrences (all)                          | 4 / 179 (2.23%)<br>4   | 9 / 360 (2.50%)<br>10  | 5 / 181 (2.76%)<br>6   |
| White blood cells urine positive<br>subjects affected / exposed<br>occurrences (all)               | 1 / 179 (0.56%)<br>1   | 5 / 360 (1.39%)<br>6   | 4 / 181 (2.21%)<br>5   |
| Nervous system disorders                                                                           |                        |                        |                        |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 179 (0.56%)<br>1   | 5 / 360 (1.39%)<br>6   | 4 / 181 (2.21%)<br>5   |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                       | 8 / 179 (4.47%)<br>10  | 12 / 360 (3.33%)<br>14 | 4 / 181 (2.21%)<br>4   |
| Blood and lymphatic system disorders                                                               |                        |                        |                        |
| Anaemia<br>subjects affected / exposed<br>occurrences (all)                                        | 8 / 179 (4.47%)<br>8   | 16 / 360 (4.44%)<br>17 | 8 / 181 (4.42%)<br>9   |
| Eye disorders                                                                                      |                        |                        |                        |
| Blepharitis - Fellow eye<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 179 (1.12%)<br>2   | 7 / 360 (1.94%)<br>7   | 5 / 181 (2.76%)<br>5   |
| Blepharitis - Study eye<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 179 (1.12%)<br>2   | 6 / 360 (1.67%)<br>6   | 4 / 181 (2.21%)<br>4   |
| Cataract - Fellow eye<br>subjects affected / exposed<br>occurrences (all)                          | 11 / 179 (6.15%)<br>11 | 27 / 360 (7.50%)<br>27 | 16 / 181 (8.84%)<br>16 |

|                                       |                   |                  |                   |
|---------------------------------------|-------------------|------------------|-------------------|
| Cataract - Study eye                  |                   |                  |                   |
| subjects affected / exposed           | 12 / 179 (6.70%)  | 31 / 360 (8.61%) | 19 / 181 (10.50%) |
| occurrences (all)                     | 12                | 32               | 20                |
| Conjunctival haemorrhage - Fellow eye |                   |                  |                   |
| subjects affected / exposed           | 1 / 179 (0.56%)   | 10 / 360 (2.78%) | 9 / 181 (4.97%)   |
| occurrences (all)                     | 1                 | 11               | 10                |
| Conjunctival haemorrhage - Study eye  |                   |                  |                   |
| subjects affected / exposed           | 9 / 179 (5.03%)   | 15 / 360 (4.17%) | 6 / 181 (3.31%)   |
| occurrences (all)                     | 9                 | 17               | 8                 |
| Diabetic retinal oedema - Fellow eye  |                   |                  |                   |
| subjects affected / exposed           | 18 / 179 (10.06%) | 34 / 360 (9.44%) | 16 / 181 (8.84%)  |
| occurrences (all)                     | 18                | 35               | 17                |
| Diabetic retinopathy - Fellow eye     |                   |                  |                   |
| subjects affected / exposed           | 5 / 179 (2.79%)   | 6 / 360 (1.67%)  | 1 / 181 (0.55%)   |
| occurrences (all)                     | 5                 | 6                | 1                 |
| Dry eye - Fellow eye                  |                   |                  |                   |
| subjects affected / exposed           | 9 / 179 (5.03%)   | 16 / 360 (4.44%) | 7 / 181 (3.87%)   |
| occurrences (all)                     | 9                 | 16               | 7                 |
| Dry eye - Study eye                   |                   |                  |                   |
| subjects affected / exposed           | 9 / 179 (5.03%)   | 18 / 360 (5.00%) | 9 / 181 (4.97%)   |
| occurrences (all)                     | 9                 | 18               | 9                 |
| Eye pain - Study eye                  |                   |                  |                   |
| subjects affected / exposed           | 6 / 179 (3.35%)   | 10 / 360 (2.78%) | 4 / 181 (2.21%)   |
| occurrences (all)                     | 7                 | 14               | 7                 |
| Eye pruritus - Fellow eye             |                   |                  |                   |
| subjects affected / exposed           | 5 / 179 (2.79%)   | 5 / 360 (1.39%)  | 0 / 181 (0.00%)   |
| occurrences (all)                     | 5                 | 5                | 0                 |
| Eye pruritus - Study eye              |                   |                  |                   |
| subjects affected / exposed           | 5 / 179 (2.79%)   | 5 / 360 (1.39%)  | 0 / 181 (0.00%)   |
| occurrences (all)                     | 5                 | 5                | 0                 |
| Macular fibrosis - Fellow eye         |                   |                  |                   |
| subjects affected / exposed           | 2 / 179 (1.12%)   | 6 / 360 (1.67%)  | 4 / 181 (2.21%)   |
| occurrences (all)                     | 2                 | 6                | 4                 |
| Macular oedema - Fellow eye           |                   |                  |                   |

|                                                                                        |                      |                        |                       |
|----------------------------------------------------------------------------------------|----------------------|------------------------|-----------------------|
| subjects affected / exposed<br>occurrences (all)                                       | 5 / 179 (2.79%)<br>9 | 8 / 360 (2.22%)<br>13  | 3 / 181 (1.66%)<br>4  |
| Vision blurred - Study eye<br>subjects affected / exposed<br>occurrences (all)         | 1 / 179 (0.56%)<br>1 | 6 / 360 (1.67%)<br>7   | 5 / 181 (2.76%)<br>6  |
| Vision blurred - Fellow eye<br>subjects affected / exposed<br>occurrences (all)        | 0 / 179 (0.00%)<br>0 | 4 / 360 (1.11%)<br>4   | 4 / 181 (2.21%)<br>4  |
| Visual acuity reduced - Fellow eye<br>subjects affected / exposed<br>occurrences (all) | 4 / 179 (2.23%)<br>5 | 7 / 360 (1.94%)<br>11  | 3 / 181 (1.66%)<br>6  |
| Visual acuity reduced - Study eye<br>subjects affected / exposed<br>occurrences (all)  | 6 / 179 (3.35%)<br>7 | 12 / 360 (3.33%)<br>18 | 6 / 181 (3.31%)<br>11 |
| Vitreous floaters - Study eye<br>subjects affected / exposed<br>occurrences (all)      | 4 / 179 (2.23%)<br>4 | 8 / 360 (2.22%)<br>9   | 4 / 181 (2.21%)<br>5  |
| Vitreous haemorrhage - Fellow eye<br>subjects affected / exposed<br>occurrences (all)  | 5 / 179 (2.79%)<br>5 | 11 / 360 (3.06%)<br>15 | 6 / 181 (3.31%)<br>10 |
| Vitreous haemorrhage - Study eye<br>subjects affected / exposed<br>occurrences (all)   | 2 / 179 (1.12%)<br>2 | 6 / 360 (1.67%)<br>11  | 4 / 181 (2.21%)<br>9  |
| Gastrointestinal disorders                                                             |                      |                        |                       |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)               | 4 / 179 (2.23%)<br>4 | 6 / 360 (1.67%)<br>7   | 2 / 181 (1.10%)<br>3  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                          | 3 / 179 (1.68%)<br>5 | 10 / 360 (2.78%)<br>13 | 7 / 181 (3.87%)<br>8  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                             | 5 / 179 (2.79%)<br>6 | 10 / 360 (2.78%)<br>11 | 5 / 181 (2.76%)<br>5  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 179 (0.00%)<br>0 | 4 / 360 (1.11%)<br>4   | 4 / 181 (2.21%)<br>4  |

|                                                 |                 |                  |                  |
|-------------------------------------------------|-----------------|------------------|------------------|
| Skin and subcutaneous tissue disorders          |                 |                  |                  |
| Diabetic foot                                   |                 |                  |                  |
| subjects affected / exposed                     | 4 / 179 (2.23%) | 7 / 360 (1.94%)  | 3 / 181 (1.66%)  |
| occurrences (all)                               | 4               | 7                | 3                |
| Renal and urinary disorders                     |                 |                  |                  |
| Chronic kidney disease                          |                 |                  |                  |
| subjects affected / exposed                     | 4 / 179 (2.23%) | 8 / 360 (2.22%)  | 4 / 181 (2.21%)  |
| occurrences (all)                               | 4               | 8                | 4                |
| Diabetic nephropathy                            |                 |                  |                  |
| subjects affected / exposed                     | 5 / 179 (2.79%) | 12 / 360 (3.33%) | 7 / 181 (3.87%)  |
| occurrences (all)                               | 5               | 12               | 7                |
| Proteinuria                                     |                 |                  |                  |
| subjects affected / exposed                     | 6 / 179 (3.35%) | 19 / 360 (5.28%) | 13 / 181 (7.18%) |
| occurrences (all)                               | 7               | 20               | 13               |
| Musculoskeletal and connective tissue disorders |                 |                  |                  |
| Arthralgia                                      |                 |                  |                  |
| subjects affected / exposed                     | 4 / 179 (2.23%) | 10 / 360 (2.78%) | 6 / 181 (3.31%)  |
| occurrences (all)                               | 4               | 12               | 8                |
| Back pain                                       |                 |                  |                  |
| subjects affected / exposed                     | 7 / 179 (3.91%) | 9 / 360 (2.50%)  | 2 / 181 (1.10%)  |
| occurrences (all)                               | 7               | 9                | 2                |
| Pain in extremity                               |                 |                  |                  |
| subjects affected / exposed                     | 0 / 179 (0.00%) | 4 / 360 (1.11%)  | 4 / 181 (2.21%)  |
| occurrences (all)                               | 0               | 4                | 4                |
| Infections and infestations                     |                 |                  |                  |
| Bronchitis                                      |                 |                  |                  |
| subjects affected / exposed                     | 7 / 179 (3.91%) | 12 / 360 (3.33%) | 5 / 181 (2.76%)  |
| occurrences (all)                               | 7               | 13               | 6                |
| COVID-19                                        |                 |                  |                  |
| subjects affected / exposed                     | 3 / 179 (1.68%) | 7 / 360 (1.94%)  | 4 / 181 (2.21%)  |
| occurrences (all)                               | 3               | 7                | 4                |
| Conjunctivitis - Fellow eye                     |                 |                  |                  |
| subjects affected / exposed                     | 4 / 179 (2.23%) | 6 / 360 (1.67%)  | 2 / 181 (1.10%)  |
| occurrences (all)                               | 4               | 6                | 2                |
| Conjunctivitis - Study eye                      |                 |                  |                  |

|                                                                                       |                        |                        |                        |
|---------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 6 / 179 (3.35%)<br>6   | 7 / 360 (1.94%)<br>7   | 1 / 181 (0.55%)<br>1   |
| Gastroenteritis<br>subjects affected / exposed<br>occurrences (all)                   | 4 / 179 (2.23%)<br>4   | 4 / 360 (1.11%)<br>4   | 0 / 181 (0.00%)<br>0   |
| Herpes zoster<br>subjects affected / exposed<br>occurrences (all)                     | 2 / 179 (1.12%)<br>2   | 7 / 360 (1.94%)<br>7   | 5 / 181 (2.76%)<br>5   |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 7 / 179 (3.91%)<br>8   | 11 / 360 (3.06%)<br>18 | 4 / 181 (2.21%)<br>10  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 16 / 179 (8.94%)<br>20 | 33 / 360 (9.17%)<br>42 | 17 / 181 (9.39%)<br>22 |
| Pulpitis dental<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 179 (1.12%)<br>2   | 6 / 360 (1.67%)<br>6   | 4 / 181 (2.21%)<br>4   |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 2 / 179 (1.12%)<br>3   | 6 / 360 (1.67%)<br>8   | 4 / 181 (2.21%)<br>5   |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 5 / 179 (2.79%)<br>5   | 8 / 360 (2.22%)<br>8   | 3 / 181 (1.66%)<br>3   |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)           | 5 / 179 (2.79%)<br>7   | 9 / 360 (2.50%)<br>12  | 4 / 181 (2.21%)<br>5   |
| Metabolism and nutrition disorders                                                    |                        |                        |                        |
| Gout<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 179 (0.56%)<br>1   | 8 / 360 (2.22%)<br>12  | 7 / 181 (3.87%)<br>11  |
| Hyperlipidaemia<br>subjects affected / exposed<br>occurrences (all)                   | 8 / 179 (4.47%)<br>8   | 10 / 360 (2.78%)<br>10 | 2 / 181 (1.10%)<br>2   |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 18 May 2018  | <p>Amendment No. 1: • Definition of "personal data" was added and "withdrawal of study consent (WOC)" was updated.</p> <ul style="list-style-type: none"><li>• Added clarification on the framework of analysis on study information collected from withdrawn subjects.</li><li>• The PK of aflibercept was removed from testing and analysis, as the pharmacokinetics data for aflibercept has been available. The PK samples are collected at approximately 24 hours after first dose and the treatment at Week 24.</li><li>• Inclusion criteria no. 5 was revised to allow enrollment of subjects with central subfield retinal thickness cutoff value on SDOCT of <math>\geq 320 \mu\text{m}</math> instead <math>\geq 340 \mu\text{m}</math>.</li><li>• The assessment schedule table was corrected according to protocol body text and adjustment of appearance for clarity.</li><li>• The contraception requirement specified in exclusion criteria no. 26 was extended from 40 days to 3 months after last dose, for consistency with the approved label of comparator in EU and US.</li><li>• Other minor corrections and clarifications.</li></ul> |
| 11 June 2020 | <p>Amendment No. 2: • Changes in relation to emerging safety issue are:</p> <ul style="list-style-type: none"><li>• Information was added to describe a new safety signal from post-marketing case reports.</li><li>• Additional guidance was added emphasizing that if any sign of intraocular inflammation is present, an IVT injection must not be performed and subjects should be treated for intraocular inflammation according to clinical practice.</li><li>• Additional examination and assessments included to fully characterize cases of intraocular inflammation were made.</li><li>• Modifications were made to include importance of Estimands per ICH E9(R1) guidance</li><li>• Changes were incorporated to address the COVID-19 pandemic</li><li>• Other changes incorporated in this amendment:</li><li>• Three endpoints were moved from Secondary to Exploratory</li><li>• Aflibercept was removed from ADA and systemic exposure</li><li>• Clarifications were added regarding unmasked investigator/site personnel, injection procedure, IOP measurement procedure, and SAE reporting period.</li></ul>                               |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com> for complete trial results.

Notes: