



## Clinical trial results:

**A 64-week, two-arm, randomized, double-masked, multicenter, phase IIIb study assessing the efficacy and safety of brolucizumab 6 mg compared to aflibercept 2 mg in a treat-to-control regimen in patients with neovascular age-related macular degeneration (TALON)**

### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2019-000716-28             |
| Trial protocol           | PT IT CZ SE GB ES BE DE NL |
| Global end of trial date | 09 September 2022          |

### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v2 (current)      |
| This version publication date  | 13 April 2024     |
| First version publication date | 16 September 2023 |
| Version creation reason        |                   |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRTH258A2303 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04005352 |
| 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                       | 09 September 2022 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 09 September 2022 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 09 September 2022 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The main objectives of this study were:

-Distribution of the last interval with no disease activity up to Week 32 (if there was disease activity, the last interval would be shortened by 4 weeks, down to a minimum of 4 weeks)

-Average change in Best-corrected visual acuity (BCVA) from baseline at Weeks 28 and 32

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.

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                          | 25 September 2019 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | No                |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 56          |
| Country: Number of subjects enrolled | Australia: 36          |
| Country: Number of subjects enrolled | Austria: 11            |
| Country: Number of subjects enrolled | Belgium: 6             |
| Country: Number of subjects enrolled | Canada: 17             |
| Country: Number of subjects enrolled | Czechia: 54            |
| Country: Number of subjects enrolled | France: 100            |
| Country: Number of subjects enrolled | Germany: 65            |
| Country: Number of subjects enrolled | United Kingdom: 13     |
| Country: Number of subjects enrolled | Israel: 22             |
| Country: Number of subjects enrolled | Italy: 28              |
| Country: Number of subjects enrolled | Korea, Republic of: 52 |
| Country: Number of subjects enrolled | Malaysia: 24           |
| Country: Number of subjects enrolled | Netherlands: 2         |

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Portugal: 25      |
| Country: Number of subjects enrolled | Spain: 98         |
| Country: Number of subjects enrolled | Sweden: 7         |
| Country: Number of subjects enrolled | Switzerland: 2    |
| Country: Number of subjects enrolled | Taiwan: 29        |
| Country: Number of subjects enrolled | United States: 87 |
| Worldwide total number of subjects   | 734               |
| EEA total number of subjects         | 396               |

Notes:

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### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 69  |
| From 65 to 84 years                       | 570 |
| 85 years and over                         | 95  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

734 participants were treated.

### 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, Monitor, Carer, Data analyst, Assessor |

### Arms

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

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

Arm description:

Intra-vitreous injection

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Brolucizumab           |
| Investigational medicinal product code | RTH258                 |
| Other name                             | Beovu                  |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravitreal use       |

Dosage and administration details:

Brolucizumab 6 mg Intravitreal injection

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

Arm description:

Intra-vitreous injection

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Aflibercept            |
| Investigational medicinal product code | J0178                  |
| Other name                             | Eylea and Zaltrap      |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravitreal use       |

Dosage and administration details:

Aflibercept 2 mg

| Number of subjects in period 1 | Brolucizumab 6 mg | Aflibercept 2 mg |
|--------------------------------|-------------------|------------------|
| Started                        | 366               | 368              |
| Completed                      | 317               | 307              |
| Not completed                  | 49                | 61               |
| Adverse event, serious fatal   | 4                 | 2                |
| Consent withdrawn by subject   | 28                | 38               |

|                          |   |    |
|--------------------------|---|----|
| Physician decision       | 7 | 13 |
| Adverse event, non-fatal | 4 | 5  |
| Lost to follow-up        | 6 | 2  |
| Protocol deviation       | - | 1  |

## Baseline characteristics

### Reporting groups

|                              |                   |
|------------------------------|-------------------|
| Reporting group title        | Brolucizumab 6 mg |
| Reporting group description: |                   |
| Intra-vitreous injection     |                   |
| Reporting group title        | Aflibercept 2 mg  |
| Reporting group description: |                   |
| Intra-vitreous injection     |                   |

| Reporting group values                    | Brolucizumab 6 mg | Aflibercept 2 mg | Total |
|-------------------------------------------|-------------------|------------------|-------|
| Number of subjects                        | 366               | 368              | 734   |
| Age Categorical                           |                   |                  |       |
| Units: Participants                       |                   |                  |       |
| <=18 years                                | 0                 | 0                | 0     |
| Between 18 and 65 years                   | 32                | 37               | 69    |
| >=65 years                                | 334               | 331              | 665   |
| Age Continuous                            |                   |                  |       |
| Units: years                              |                   |                  |       |
| arithmetic mean                           | 75.5              | 75.5             |       |
| standard deviation                        | ± 7.85            | ± 8.41           | -     |
| Sex: Female, Male                         |                   |                  |       |
| Units: Participants                       |                   |                  |       |
| Female                                    | 216               | 204              | 420   |
| Male                                      | 150               | 164              | 314   |
| Race (NIH/OMB)                            |                   |                  |       |
| Units: Subjects                           |                   |                  |       |
| American Indian or Alaska Native          | 0                 | 0                | 0     |
| Asian                                     | 55                | 55               | 110   |
| Native Hawaiian or Other Pacific Islander | 0                 | 0                | 0     |
| Black or African American                 | 1                 | 1                | 2     |
| White                                     | 310               | 312              | 622   |
| More than one race                        | 0                 | 0                | 0     |
| Unknown or Not Reported                   | 0                 | 0                | 0     |

## End points

### End points reporting groups

|                              |                   |
|------------------------------|-------------------|
| Reporting group title        | Brolucizumab 6 mg |
| Reporting group description: |                   |
| Intra-vitreous injection     |                   |
| Reporting group title        | Aflibercept 2 mg  |
| Reporting group description: |                   |
| Intra-vitreous injection     |                   |

### Primary: Distribution of the last interval with no disease activity up to Week 32 - study eye

|                                                                                                                                                                                                                                                                        |                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                        | Distribution of the last interval with no disease activity up to Week 32 - study eye |
| End point description:                                                                                                                                                                                                                                                 |                                                                                      |
| No disease activity is defined as no change in visual acuity and no change in other signs of the disease (e.g. Intraretinal Fluid (IRF), Subretinal Fluid (SRF), hemorrhage, leakage, etc.).                                                                           |                                                                                      |
| Treatment interval distribution. Number (%) of subjects at 12/8/4-weeks intervals up to Week 32 for the study eye.                                                                                                                                                     |                                                                                      |
| If the study treatment is discontinued before Week 16, then the treatment interval is 4 weeks; otherwise, the last interval with no disease activity is used (if there was disease activity, the last interval is shortened by 4 weeks, down to a minimum of 4 weeks). |                                                                                      |
| If the duration of the last interval falls within the following ranges of (4-week, 8-week) or (8-week, 12-week) or $\geq 12$ -week then the floor value of these ranges was used.                                                                                      |                                                                                      |
| End point type                                                                                                                                                                                                                                                         | Primary                                                                              |
| End point timeframe:                                                                                                                                                                                                                                                   |                                                                                      |
| Up to Week 32                                                                                                                                                                                                                                                          |                                                                                      |

| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 366               | 368              |  |  |
| Units: Participants         |                   |                  |  |  |
| 12 weeks                    | 141               | 73               |  |  |
| 8 weeks                     | 131               | 147              |  |  |
| 4 weeks                     | 94                | 148              |  |  |

### Statistical analyses

|                            |                                      |
|----------------------------|--------------------------------------|
| Statistical analysis title | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups          | Brolucizumab 6 mg v Aflibercept 2 mg |

|                                         |                         |
|-----------------------------------------|-------------------------|
| Number of subjects included in analysis | 734                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | < 0.0001 <sup>[1]</sup> |
| Method                                  | Wilcoxon (Mann-Whitney) |

Notes:

[1] - with significance level of 0.025

### Primary: Average change from baseline at Week 28 and Week 32 in Best-corrected visual acuity (BCVA) - study eye

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Average change from baseline at Week 28 and Week 32 in Best-corrected visual acuity (BCVA) - study eye |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.

Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

Least squares mean estimate - for weeks 28 and 32 combined.

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

End point timeframe:

Baseline, Week 28 and Week 32

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 366               | 368              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) | 5.2 (± 0.51)      | 5.1 (± 0.51)     |  |  |

### Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | < 0.0001                             |
| Method                                  | ANOVA                                |
| Parameter estimate                      | Difference                           |
| Point estimate                          | 0.1                                  |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -1.3                                 |
| upper limit                             | 1.5                                  |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 0.73                                 |

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**Secondary: Distribution of the last interval with no disease activity up to Week 64 - study eye**

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|                 |                                                                                      |
|-----------------|--------------------------------------------------------------------------------------|
| End point title | Distribution of the last interval with no disease activity up to Week 64 - study eye |
|-----------------|--------------------------------------------------------------------------------------|

End point description:

No disease activity is defined as no change in visual acuity and no change in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

Treatment interval distribution. The number of subjects at 16/12/8/4-weeks intervals as the last interval with no disease activity.

If the study treatment is discontinued before Week 16, then the treatment interval is 4 weeks; otherwise, the last interval with no disease activity is used (if there was disease activity, the last interval is shortened by 4 weeks, down to a minimum of 4 weeks).

If the duration of the last interval falls within the following ranges of (4-week, 8-week) or (8-week, 12-week) or (12-weeks, 16-weeks) or  $\geq 16$ -week then the floor value of these ranges was used.

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

End point timeframe:

Up to Week 64

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| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 366               | 368              |  |  |
| Units: Participants         |                   |                  |  |  |
| 16 Weeks                    | 104               | 45               |  |  |
| 12 Weeks                    | 82                | 88               |  |  |
| 8 Weeks                     | 95                | 81               |  |  |
| 4 Weeks                     | 85                | 154              |  |  |

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**Statistical analyses**

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|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | < 0.0001                             |
| Method                                  | Wilcoxon (Mann-Whitney)              |

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**Secondary: Distribution of the maximal intervals with no disease activity up to Week 64 - study eye**

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|                 |                                                                   |
|-----------------|-------------------------------------------------------------------|
| End point title | Distribution of the maximal intervals with no disease activity up |
|-----------------|-------------------------------------------------------------------|

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**End point description:**

No disease activity is defined as no change in visual acuity and no change in other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

Maximal interval distribution. Number of subjects at 16/12/8/4-weeks intervals as the last interval with no disease activity.

If the study treatment is discontinued before Week 16 included, then the treatment interval is 4 weeks; otherwise, the last interval with no disease activity is used (if there was disease activity, the last interval is shortened by 4 weeks, down to a minimum of 4 weeks).

If the duration of the maximal interval falls within the following ranges of [4-weeks, 8-weeks) or [8-weeks, 12-weeks) or [12-weeks, 16-weeks] or  $\geq 16$ -weeks then the floor value of these ranges is used.

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

End point timeframe:

Up to Week 64

| <b>End point values</b>     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 366               | 368              |  |  |
| Units: Participants         |                   |                  |  |  |
| 16 Weeks                    | 117               | 57               |  |  |
| 12 Weeks                    | 96                | 92               |  |  |
| 8 Weeks                     | 94                | 114              |  |  |
| 4 Weeks                     | 59                | 105              |  |  |

**Statistical analyses**

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | < 0.0001                             |
| Method                                  | Wilcoxon (Mann-Whitney)              |

**Secondary: Number of participants with no disease activity - study eye**

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Number of participants with no disease activity - study eye |
|-----------------|-------------------------------------------------------------|

**End point description:**

Disease activity assessment as determined by visual acuity and assessment of other signs of the disease (e.g. IRF, SRF, hemorrhage, leakage, etc.).

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

End point timeframe:

Weeks 14 and 16

| <b>End point values</b>     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 301               | 296              |  |  |
| Units: Participants         |                   |                  |  |  |
| Week 14 (n=118, 137)        | 87                | 88               |  |  |
| Week 16 (n=301,296)         | 260               | 211              |  |  |

### Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 597                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | < 0.0001                             |
| Method                                  | likelihood ratio test                |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 2.6                                  |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 1.7                                  |
| upper limit                             | 3.9                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 597                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.051                              |
| Method                                  | likelihood ratio test                |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 1.6                                  |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 0.9                                  |
| upper limit                             | 2.7                                  |

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**Secondary: Time from Last Loading Injection to First Visit with No Disease Activity (Weeks) - 75th percentile - study eye**

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|                 |                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Time from Last Loading Injection to First Visit with No Disease Activity (Weeks) - 75th percentile - study eye |
|-----------------|----------------------------------------------------------------------------------------------------------------|

End point description:

Intraretinal fluid (IRF) and subretinal fluid (SRF) were assessed by Spectral Domain Optical Coherence Tomography (SD-OCT) (study eye).

Please note that this endpoint can be impacted by the optional disease activity assessment visits and the flexible dosing regimen, in addition to the randomized treatment. Hence, the observed treatment effect may be confounded by the study design artifacts.

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

End point timeframe:

Up to Week 64

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| End point values                 | Brolucizumab 6 mg | Aflibercept 2 mg    |  |  |
|----------------------------------|-------------------|---------------------|--|--|
| Subject group type               | Reporting group   | Reporting group     |  |  |
| Number of subjects analysed      | 366               | 368                 |  |  |
| Units: weeks                     |                   |                     |  |  |
| number (confidence interval 95%) |                   |                     |  |  |
| 75th percentile                  | 9.1 (8.9 to 10.6) | 12.1 (11.3 to 12.9) |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Time-to-first dry retina - time to the first visit with no Intraretinal Fluid (IRF) or Subretinal Fluid (SRF) - study eye**

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|                 |                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Time-to-first dry retina - time to the first visit with no Intraretinal Fluid (IRF) or Subretinal Fluid (SRF) - study eye |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|

End point description:

Intraretinal fluid (IRF) and subretinal fluid (SRF) were assessed by Spectral Domain Optical Coherence Tomography (SD-OCT) (study eye).

Includes subjects with no important protocol deviations with impact.

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

End point timeframe:

Up to Week 64

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| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 330               | 337              |  |  |
| Units: Participants         |                   |                  |  |  |
| 0 Week                      | 330               | 337              |  |  |
| 4 Week                      | 144               | 138              |  |  |
| 8 Week                      | 70                | 86               |  |  |
| 12 Week                     | 70                | 86               |  |  |
| 16 Week                     | 37                | 67               |  |  |
| 20 Week                     | 34                | 55               |  |  |
| 24 Week                     | 30                | 47               |  |  |
| 28 Week                     | 28                | 38               |  |  |
| 32 Week                     | 20                | 25               |  |  |
| 36 Week                     | 20                | 23               |  |  |
| 40 Week                     | 18                | 22               |  |  |
| 44 Week                     | 18                | 22               |  |  |
| 48 Week                     | 17                | 20               |  |  |
| 52 Week                     | 17                | 20               |  |  |
| 56 Week                     | 17                | 20               |  |  |
| 60 Week                     | 11                | 14               |  |  |
| 64 Week                     | 0                 | 0                |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Average change from baseline at Week 60 and Week 64 in Best-corrected visual acuity (BCVA) - study eye

|                 |                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------|
| End point title | Average change from baseline at Week 60 and Week 64 in Best-corrected visual acuity (BCVA) - study eye |
|-----------------|--------------------------------------------------------------------------------------------------------|

End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.

Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

Least squares mean estimate - for weeks 60 and 64 combined.

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

End point timeframe:

Baseline, Week 60 and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 366               | 368              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) | 4.7 (± 0.60)      | 4.9 (± 0.60)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.8137 <sup>[2]</sup>              |
| Method                                  | ANOVA                                |
| Parameter estimate                      | Difference                           |
| Point estimate                          | -0.2                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -1.9                                 |
| upper limit                             | 1.5                                  |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 0.84                                 |

Notes:

[2] - p-value for treatment difference

## Secondary: Number of participants with best-corrected visual acuity improvements of $\geq 15$ letters in BCVA from baseline or reached BCVA $\geq 84$ letters up to Week 32/64 per treatment arm - study eye

|                 |                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with best-corrected visual acuity improvements of $\geq 15$ letters in BCVA from baseline or reached BCVA $\geq 84$ letters up to Week 32/64 per treatment arm - study eye |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.

Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning.

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

End point timeframe:

Baseline, Week 32, and Week 64

|                             |                   |                  |  |  |
|-----------------------------|-------------------|------------------|--|--|
| <b>End point values</b>     | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 366               | 368              |  |  |
| Units: participants         |                   |                  |  |  |
| Week 32                     | 88                | 92               |  |  |
| Week 64                     | 89                | 91               |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.4667                             |
| Method                                  | likelihood ratio test                |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 1                                    |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 0.7                                  |
| upper limit                             | 1.4                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.4106                             |
| Method                                  | likelihood ratio test                |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 1                                    |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 0.7                                  |
| upper limit                             | 1.3                                  |

## Secondary: Number of participants with best-corrected visual acuity $\geq$ 69 letters - study eye

|                                                                                                          |                                                                                        |
|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| End point title                                                                                          | Number of participants with best-corrected visual acuity $\geq$ 69 letters - study eye |
| End point description:                                                                                   |                                                                                        |
| BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts. |                                                                                        |
| Min and max possible scores are 0-100 respectively. A higher score represents better visual functioning. |                                                                                        |
| End point type                                                                                           | Secondary                                                                              |

End point timeframe:  
Week 32 and Week 64

| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 366               | 368              |  |  |
| Units: Participants         |                   |                  |  |  |
| Week 32                     | 244               | 228              |  |  |
| Week 64                     | 240               | 219              |  |  |

### Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.115                              |
| Method                                  | likelihood ratio test                |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 1.2                                  |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 0.9                                  |
| upper limit                             | 1.8                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.2397                             |
| Method                                  | likelihood ratio test                |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 1.1                                  |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 0.8                                  |
| upper limit                             | 1.7                                  |

---

**Secondary: Average change from baseline in Central Subfield Thickness (CSFT) - study eye**

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|                 |                                                                               |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Average change from baseline in Central Subfield Thickness (CSFT) - study eye |
|-----------------|-------------------------------------------------------------------------------|

End point description:

CSFT was measured by Spectral Domain Optical Coherence Tomography

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

End point timeframe:

Baseline, Weeks 28 and 32 and at Weeks 60 and 64

---

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 366               | 368              |  |  |
| Units: micrometers                  |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Weeks 28 and 32 (average)           | -166.9 (± 6.97)   | -140.0 (± 6.96)  |  |  |
| Weeks 60 and 64 (average)           | -182.9 (± 7.72)   | -167.5 (± 8.16)  |  |  |

**Statistical analyses**

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 734                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.0066                             |
| Method                                  | ANOVA                                |
| Parameter estimate                      | Difference                           |
| Point estimate                          | -26.9                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -46.3                                |
| upper limit                             | -7.5                                 |
| Variability estimate                    | Standard error of the mean           |
| Dispersion value                        | 9.87                                 |

---

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

---

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 734                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           |                            |
| P-value                                 | = 0.1714                   |
| Method                                  | ANOVA                      |
| Parameter estimate                      | Difference                 |
| Point estimate                          | -15.4                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -37.6                      |
| upper limit                             | 6.7                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 11.26                      |

---

**Secondary: Number of participants with presence of Intraretinal Fluid and/or Subretinal Fluid in the central subfield - study eye**

|                                                                                                                          |                                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                          | Number of participants with presence of Intraretinal Fluid and/or Subretinal Fluid in the central subfield - study eye |
| End point description:                                                                                                   |                                                                                                                        |
| Intraretinal Fluid and/or Subretinal Fluid status was measured by Spectral Domain Optical Coherence Tomography (SD-OCT). |                                                                                                                        |
| End point type                                                                                                           | Secondary                                                                                                              |
| End point timeframe:                                                                                                     |                                                                                                                        |
| At Weeks 28, 32, 60 and 64                                                                                               |                                                                                                                        |

| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 286               | 289              |  |  |
| Units: Participants         |                   |                  |  |  |
| Week 28 (n=285,289)         | 175               | 198              |  |  |
| Week 32 (n=286, 267)        | 144               | 152              |  |  |
| Week 60 (n=269,244)         | 60                | 69               |  |  |
| Week 64 (n=271, 241)        | 72                | 83               |  |  |

**Statistical analyses**

No statistical analyses for this end point

---

**Secondary: Number of participants with presence of sub-Retinal Pigment Epithelium fluid in the central subfield - study eye**

|                 |                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with presence of sub-Retinal Pigment Epithelium fluid in the central subfield - study eye |
|-----------------|------------------------------------------------------------------------------------------------------------------|

End point description:

Sub-Retinal Pigment Epithelium fluid status was measured by Spectral Domain Optical Coherence Tomography (SD-OCT).

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

End point timeframe:

At Weeks 28, 32, 60 and 64

| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 288               | 289              |  |  |
| Units: Participants         |                   |                  |  |  |
| Week 28 (n=288,289)         | 173               | 208              |  |  |
| Week 32 (n=288, 266)        | 156               | 175              |  |  |
| Week 60 (n=271,244)         | 27                | 31               |  |  |
| Week 64 (n=271, 242)        | 34                | 43               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - Composite scores - study eye

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - Composite scores - study eye |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. A composite score is derived based on the average of the 11 subscales.

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

End point timeframe:

Baseline, Week 32, and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 4.09 (± 0.20)     | 3.72 (± 0.21)    |  |  |
| Week 64 (n=248, 224)                | 2.8 (± 0.69)      | 4.7 (± 0.73)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.052                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -2                                   |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -3.9                                 |
| upper limit                             | 0                                    |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.193                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 0.37                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -0.2                                 |
| upper limit                             | 0.9                                  |

## Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - General Vision - study eye

|                 |                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - General Vision - study eye |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

### End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a

high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

|                                |           |
|--------------------------------|-----------|
| End point type                 | Secondary |
| End point timeframe:           |           |
| Baseline, Week 32, and Week 64 |           |

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 7.94 (± 0.86)     | 5.79 (± 0.89)    |  |  |
| Week 64 (n=248, 224)                | 7.3 (± 0.87)      | 8.0 (± 0.92)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.081                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 2.16                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -0.3                                 |
| upper limit                             | 4.6                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.59                               |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -0.7                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -3.2    |
| upper limit         | 1.8     |

## Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Ocular Pain - study eye

|                 |                                                                                                              |
|-----------------|--------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Ocular Pain - study eye |
|-----------------|--------------------------------------------------------------------------------------------------------------|

End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

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

End point timeframe:

Baseline, Week 32, and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 3.55 (± 0.92)     | 2.78 (± 0.94)    |  |  |
| Week 64 (n=248, 224)                | 3.1 (± 0.89)      | 5.0 (± 0.94)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.138                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -1.9                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -4.5    |
| upper limit         | 0.6     |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.558                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 0.77                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -1.8                                 |
| upper limit                             | 3.4                                  |

### Secondary: Change from baseline n Visual Function Questionnaire-25 (VFQ-25) - subscale score - Near Activities - study eye

|                 |                                                                                                                 |
|-----------------|-----------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline n Visual Function Questionnaire-25 (VFQ-25) - subscale score - Near Activities - study eye |
|-----------------|-----------------------------------------------------------------------------------------------------------------|

End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

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

End point timeframe:

Baseline, Week 32, and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 7.46 (± 1.05)     | 5.86 (± 1.08)    |  |  |
| Week 64 (n=248, 224)                | 4.9 (± 1.12)      | 7.9 (± 1.18)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.07                               |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -3                                   |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -6.2                                 |
| upper limit                             | 0.2                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.287                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 1.6                                  |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -1.4                                 |
| upper limit                             | 4.6                                  |

## Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Distance Activities - study eye

|                 |                                                                                                                      |
|-----------------|----------------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Distance Activities - study eye |
|-----------------|----------------------------------------------------------------------------------------------------------------------|

### End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a

high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

|                                |           |
|--------------------------------|-----------|
| End point type                 | Secondary |
| End point timeframe:           |           |
| Baseline, Week 32, and Week 64 |           |

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 3.06 (± 0.95)     | 3.78 (± 0.98)    |  |  |
| Week 64 (n=248, 224)                | 2.5 (± 0.99)      | 5.0 (± 1.04)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.086                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -2.5                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -5.3                                 |
| upper limit                             | 0.4                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.602                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -0.71                                |

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

## Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Social Functioning - study eye

|                 |                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Social Functioning - study eye |
|-----------------|---------------------------------------------------------------------------------------------------------------------|

### End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning or outcome. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

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

### End point timeframe:

Baseline, Week 32, and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 1.99 (± 0.79)     | 0.43 (± 0.82)    |  |  |
| Week 64 (n=248, 224)                | 0.2 (± 0.81)      | 1.7 (± 0.85)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.21                               |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -1.5                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -3.8    |
| upper limit         | 0.8     |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.174                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 1.55                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -0.7                                 |
| upper limit                             | 3.8                                  |

### Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Mental Health - study eye

|                 |                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Mental Health - study eye |
|-----------------|----------------------------------------------------------------------------------------------------------------|

End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning or outcome. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

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

End point timeframe:

Baseline, Week 32, and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 5.83 (± 0.99)     | 6.79 (± 1.02)    |  |  |
| Week 64 (n=248, 224)                | 5.0 (± 1.08)      | 7.2 (± 1.14)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.147                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -2.3                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -5.4                                 |
| upper limit                             | 0.8                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.499                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -0.96                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -3.8                                 |
| upper limit                             | 1.8                                  |

## Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Role Difficulties - study eye

|                 |                                                                                                                    |
|-----------------|--------------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Role Difficulties - study eye |
|-----------------|--------------------------------------------------------------------------------------------------------------------|

### End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a

high score represents better visual functioning or outcome. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

|                                |           |
|--------------------------------|-----------|
| End point type                 | Secondary |
| End point timeframe:           |           |
| Baseline, Week 32, and Week 64 |           |

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 5.17 (± 1.31)     | 4.30 (± 1.35)    |  |  |
| Week 64 (n=248, 224)                | 4.7 (± 1.31)      | 5.9 (± 1.38)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.507                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -1.3                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -5                                   |
| upper limit                             | 2.5                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.643                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 0.88                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -2.8    |
| upper limit         | 4.6     |

## Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Dependency - study eye

|                 |                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Dependency - study eye |
|-----------------|-------------------------------------------------------------------------------------------------------------|

### End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning or outcome. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

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

### End point timeframe:

Baseline, Week 32, and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 2.71 (± 0.88)     | 2.22 (± 0.91)    |  |  |
| Week 64 (n=248, 224)                | -0.6 (± 1.09)     | 2.2 (± 1.14)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.07                               |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -2.9                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -6      |
| upper limit         | 0.2     |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.7                                |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 0.49                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -2                                   |
| upper limit                             | 3                                    |

### Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Driving - study eye

|                 |                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Driving - study eye |
|-----------------|----------------------------------------------------------------------------------------------------------|

End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

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

End point timeframe:

Baseline, Week 32, and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 4.92 (± 1.56)     | 4.19 (± 1.57)    |  |  |
| Week 64 (n=248, 224)                | 1.3 (± 1.74)      | 3.0 (± 1.79)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.494                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -1.7                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -6.6                                 |
| upper limit                             | 3.2                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.741                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 0.73                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -3.6                                 |
| upper limit                             | 5.1                                  |

## Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Color Vision - study eye

|                 |                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Color Vision - study eye |
|-----------------|---------------------------------------------------------------------------------------------------------------|

### End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a

high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

|                                |           |
|--------------------------------|-----------|
| End point type                 | Secondary |
| End point timeframe:           |           |
| Baseline, Week 32, and Week 64 |           |

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 1.78 (± 0.63)     | 0.02 (± 0.65)    |  |  |
| Week 64 (n=248, 224)                | 0.1 (± 0.80)      | 1.2 (± 0.84)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.331                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -1.1                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -3.4                                 |
| upper limit                             | 1.2                                  |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.054                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 1.76                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0       |
| upper limit         | 3.5     |

## Secondary: Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Peripheral Vision - study eye

|                 |                                                                                                                    |
|-----------------|--------------------------------------------------------------------------------------------------------------------|
| End point title | Change from baseline in Visual Function Questionnaire-25 (VFQ-25) - subscale score - Peripheral Vision - study eye |
|-----------------|--------------------------------------------------------------------------------------------------------------------|

### End point description:

The National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) measures the influence of visual disability and visual symptoms on general health domains.

The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better visual functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively.

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

### End point timeframe:

Baseline, Week 32, and Week 64

| End point values                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-------------------------------------|-------------------|------------------|--|--|
| Subject group type                  | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed         | 278               | 261              |  |  |
| Units: Scores on a scale            |                   |                  |  |  |
| least squares mean (standard error) |                   |                  |  |  |
| Week 32 (n=278, 261)                | 3.24 (± 1.01)     | 2.00 (± 1.04)    |  |  |
| Week 64 (n=248, 224)                | 2.5 (± 1.08)      | 3.0 (± 1.13)     |  |  |

## Statistical analyses

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| Statistical analysis title              | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.728                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | -0.5                                 |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -3.6    |
| upper limit         | 2.5     |

|                                         |                                      |
|-----------------------------------------|--------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Comparison groups                       | Brolucizumab 6 mg v Aflibercept 2 mg |
| Number of subjects included in analysis | 539                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           |                                      |
| P-value                                 | = 0.394                              |
| Method                                  | ANCOVA                               |
| Parameter estimate                      | LS Mean Difference                   |
| Point estimate                          | 1.24                                 |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | -1.6                                 |
| upper limit                             | 4.1                                  |

**Secondary: Number of participants with treatment emergent ocular adverse events (greater than or equal to 1% in any treatment arm) by preferred term for the study eye**

|                 |                                                                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with treatment emergent ocular adverse events (greater than or equal to 1% in any treatment arm) by preferred term for the study eye |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject.

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

End point timeframe:

Adverse events are reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 483 days, approx. 69 weeks, 1.3 years.

| <b>End point values</b>                    | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|--------------------------------------------|-------------------|------------------|--|--|
| Subject group type                         | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed                | 366               | 368              |  |  |
| Units: Participants                        |                   |                  |  |  |
| Number of subjects with at least one event | 114               | 102              |  |  |
| Conjunctival haemorrhage                   | 23                | 13               |  |  |
| Visual acuity reduced                      | 16                | 18               |  |  |
| Eye pain                                   | 17                | 13               |  |  |

|                                              |    |    |  |  |
|----------------------------------------------|----|----|--|--|
| Vitreous floaters                            | 12 | 6  |  |  |
| Intraocular pressure increased               | 5  | 11 |  |  |
| Subretinal fluid                             | 5  | 11 |  |  |
| Vitreous detachment                          | 10 | 3  |  |  |
| Retinal haemorrhage                          | 4  | 7  |  |  |
| Cataract                                     | 5  | 5  |  |  |
| Foreign body sensation in eyes               | 4  | 6  |  |  |
| Intra-ocular injection complication          | 6  | 3  |  |  |
| Retinal pigment epithelial tear              | 5  | 4  |  |  |
| Macular oedema                               | 3  | 4  |  |  |
| Posterior capsule opacification              | 2  | 5  |  |  |
| Dry eye                                      | 2  | 4  |  |  |
| Hordeolum                                    | 4  | 2  |  |  |
| Neovascular age-related macular degeneration | 2  | 4  |  |  |
| Retinal oedema                               | 1  | 4  |  |  |
| Uveitis                                      | 4  | 1  |  |  |
| Vision blurred                               | 4  | 1  |  |  |
| Detachment of retinal pigment epithelium     | 0  | 4  |  |  |
| Retinal artery occlusion                     | 4  | 0  |  |  |
| Subretinal fibrosis                          | 4  | 0  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with treatment emergent non-ocular adverse events (greater than or equal to 2% in any treatment arm) - summary table

|                 |                                                                                                                                             |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with treatment emergent non-ocular adverse events (greater than or equal to 2% in any treatment arm) - summary table |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject.

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

End point timeframe:

Adverse events are reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 483 days, approx. 69 weeks, 1.3 years.

| End point values            | Brolucizumab 6 mg | Aflibercept 2 mg |  |  |
|-----------------------------|-------------------|------------------|--|--|
| Subject group type          | Reporting group   | Reporting group  |  |  |
| Number of subjects analysed | 366               | 368              |  |  |
| Units: Participants         | 182               | 185              |  |  |

## **Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 483 days, approx. 69 weeks, 1.3 years.

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 | 25.0 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Brolucizumab 6mg

|                       |              |
|-----------------------|--------------|
| Reporting group title | All Patients |
|-----------------------|--------------|

Reporting group description:

All Patients

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

Reporting group description:

Aflibercept 2mg

| Serious adverse events                                              | Brolucizumab 6mg  | All Patients       | Aflibercept 2mg   |
|---------------------------------------------------------------------|-------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                    |                   |
| subjects affected / exposed                                         | 58 / 366 (15.85%) | 111 / 734 (15.12%) | 53 / 368 (14.40%) |
| number of deaths (all causes)                                       | 4                 | 6                  | 2                 |
| number of deaths resulting from adverse events                      | 0                 | 0                  | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                    |                   |
| Hepatic cancer                                                      |                   |                    |                   |
| subjects affected / exposed                                         | 1 / 366 (0.27%)   | 1 / 734 (0.14%)    | 0 / 368 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 1              | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0              | 0 / 0             |
| Colon cancer                                                        |                   |                    |                   |
| subjects affected / exposed                                         | 1 / 366 (0.27%)   | 3 / 734 (0.41%)    | 2 / 368 (0.54%)   |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 3              | 0 / 2             |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0              | 0 / 0             |
| Breast cancer                                                       |                   |                    |                   |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anal cancer                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Adenocarcinoma gastric                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung neoplasm                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tongue neoplasm malignant stage unspecified     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Squamous cell carcinoma                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatic carcinoma                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-small cell lung cancer metastatic           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Neoplasm                                        |                 |                 |                 |

|                                                      |                 |                 |                 |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastatic squamous cell carcinoma                   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal neoplasm                                       |                 |                 |                 |
| subjects affected / exposed                          | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| 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                                   |                 |                 |                 |
| Deep vein thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive crisis                                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic stenosis                                      |                 |                 |                 |
| subjects affected / exposed                          | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral arterial occlusive disease                |                 |                 |                 |
| subjects affected / exposed                          | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| 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 artery aneurysm rupture                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 1           | 0 / 1           |
| General disorders and administration site conditions |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Chest discomfort                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Immune system disorders                         |                 |                 |                 |
| Anaphylactic shock                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Dyspnoea exertional                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Epistaxis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Hypercapnia                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Pneumonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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 / 366 (0.00%) | 2 / 734 (0.27%) | 2 / 368 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                       |                 |                 |                 |
|-------------------------------------------------------|-----------------|-----------------|-----------------|
| Pulmonary oedema                                      |                 |                 |                 |
| subjects affected / exposed                           | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                                 |                 |                 |                 |
| Psychotic disorder due to a general medical condition |                 |                 |                 |
| subjects affected / exposed                           | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Abnormal behaviour                                    |                 |                 |                 |
| subjects affected / exposed                           | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| 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                                        |                 |                 |                 |
| Intraocular pressure increased - Study Eye            |                 |                 |                 |
| subjects affected / exposed                           | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all       | 0 / 0           | 1 / 2           | 1 / 2           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications        |                 |                 |                 |
| Face injury                                           |                 |                 |                 |
| subjects affected / exposed                           | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Facial bones fracture                                 |                 |                 |                 |
| subjects affected / exposed                           | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall                                                  |                 |                 |                 |
| subjects affected / exposed                           | 0 / 366 (0.00%) | 2 / 734 (0.27%) | 2 / 368 (0.54%) |
| occurrences causally related to treatment / all       | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all            | 0 / 0           | 0 / 0           | 0 / 0           |
| Femoral neck fracture                                 |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 366 (0.55%) | 3 / 734 (0.41%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Craniocerebral injury                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Concussion                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervical vertebral fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 2 / 734 (0.27%) | 2 / 368 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Forearm fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Incisional hernia                               |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Meniscus injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Radius fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Stress fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thoracic vertebral fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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                     | 2 / 366 (0.55%) | 2 / 734 (0.27%) | 0 / 368 (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           |
| Cardiac disorders                               |                 |                 |                 |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 366 (0.55%) | 2 / 734 (0.27%) | 0 / 368 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 3 / 366 (0.82%) | 4 / 734 (0.54%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 8           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Arrhythmia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| 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                     | 2 / 366 (0.55%) | 2 / 734 (0.27%) | 0 / 368 (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           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 3 / 734 (0.41%) | 2 / 368 (0.54%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Tachycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Sinus node dysfunction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Myocardial ischaemia                            |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 2 / 366 (0.55%) | 3 / 734 (0.41%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Carotid artery stenosis                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Basal ganglia infarction                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Cerebral infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Speech disorder                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Iron deficiency anaemia                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo positional                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Eye disorders                                   |                 |                 |                 |
| Glaucoma - Study Eye                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye inflammation - Study Eye                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Iridocyclitis - Study Eye                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 2 / 2           | 2 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Visual acuity reduced - Study Eye               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Uveitis - Study Eye                             |                 |                 |                 |
| subjects affected / exposed                     | 3 / 366 (0.82%) | 3 / 734 (0.41%) | 0 / 368 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3           | 3 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal vein occlusion - Study Eye              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal vascular occlusion - Study Eye          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Macular hole - Study Eye                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Ocular discomfort - Study Eye                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Ocular discomfort - Fellow Eye                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Gastrointestinal disorders                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Abdominal adhesions                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Ileus paralytic                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gingival bleeding                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Ureterolithiasis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| 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 kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| 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 |                 |                 |                 |
| Spondylolisthesis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spinal stenosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Neck pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 2 / 734 (0.27%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 366 (0.55%) | 2 / 734 (0.27%) | 0 / 368 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Escherichia sepsis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 2 / 734 (0.27%) | 2 / 368 (0.54%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19 pneumonia                              |                 |                 |                 |
| subjects affected / exposed                     | 5 / 366 (1.37%) | 6 / 734 (0.82%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 6           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| COVID-19                                        |                 |                 |                 |
| subjects affected / exposed                     | 2 / 366 (0.55%) | 2 / 734 (0.27%) | 0 / 368 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Endophthalmitis - Study Eye                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| 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 viral                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Cachexia                                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 366 (0.27%) | 1 / 734 (0.14%) | 0 / 368 (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           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 366 (0.00%) | 1 / 734 (0.14%) | 1 / 368 (0.27%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

Frequency threshold for reporting non-serious adverse events: 1 %

| <b>Non-serious adverse events</b>                     | Brolucizumab 6mg   | All Patients       | Aflibercept 2mg    |
|-------------------------------------------------------|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                    |                    |
| subjects affected / exposed                           | 172 / 366 (46.99%) | 349 / 734 (47.55%) | 177 / 368 (48.10%) |
| Vascular disorders                                    |                    |                    |                    |
| Hypertension                                          |                    |                    |                    |
| subjects affected / exposed                           | 18 / 366 (4.92%)   | 35 / 734 (4.77%)   | 17 / 368 (4.62%)   |
| occurrences (all)                                     | 19                 | 37                 | 18                 |
| Respiratory, thoracic and mediastinal disorders       |                    |                    |                    |
| Cough                                                 |                    |                    |                    |
| subjects affected / exposed                           | 4 / 366 (1.09%)    | 7 / 734 (0.95%)    | 3 / 368 (0.82%)    |
| occurrences (all)                                     | 4                  | 7                  | 3                  |
| Psychiatric disorders                                 |                    |                    |                    |
| Anxiety                                               |                    |                    |                    |
| subjects affected / exposed                           | 5 / 366 (1.37%)    | 5 / 734 (0.68%)    | 0 / 368 (0.00%)    |
| occurrences (all)                                     | 6                  | 6                  | 0                  |
| Investigations                                        |                    |                    |                    |
| Intraocular pressure increased - Study Eye            |                    |                    |                    |
| subjects affected / exposed                           | 5 / 366 (1.37%)    | 15 / 734 (2.04%)   | 10 / 368 (2.72%)   |
| occurrences (all)                                     | 6                  | 22                 | 16                 |
| Gamma-glutamyltransferase increased                   |                    |                    |                    |

|                                                  |                      |                      |                      |
|--------------------------------------------------|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 4 / 366 (1.09%)<br>4 | 7 / 734 (0.95%)<br>7 | 3 / 368 (0.82%)<br>3 |
| Injury, poisoning and procedural complications   |                      |                      |                      |
| Vaccination complication                         |                      |                      |                      |
| subjects affected / exposed                      | 3 / 366 (0.82%)      | 7 / 734 (0.95%)      | 4 / 368 (1.09%)      |
| occurrences (all)                                | 3                    | 7                    | 4                    |
| Intra-ocular injection complication - Study Eye  |                      |                      |                      |
| subjects affected / exposed                      | 6 / 366 (1.64%)      | 9 / 734 (1.23%)      | 3 / 368 (0.82%)      |
| occurrences (all)                                | 7                    | 11                   | 4                    |
| Fall                                             |                      |                      |                      |
| subjects affected / exposed                      | 6 / 366 (1.64%)      | 15 / 734 (2.04%)     | 9 / 368 (2.45%)      |
| occurrences (all)                                | 6                    | 18                   | 12                   |
| Cardiac disorders                                |                      |                      |                      |
| Atrial fibrillation                              |                      |                      |                      |
| subjects affected / exposed                      | 6 / 366 (1.64%)      | 7 / 734 (0.95%)      | 1 / 368 (0.27%)      |
| occurrences (all)                                | 6                    | 7                    | 1                    |
| Nervous system disorders                         |                      |                      |                      |
| Carpal tunnel syndrome                           |                      |                      |                      |
| subjects affected / exposed                      | 4 / 366 (1.09%)      | 4 / 734 (0.54%)      | 0 / 368 (0.00%)      |
| occurrences (all)                                | 4                    | 4                    | 0                    |
| Dizziness                                        |                      |                      |                      |
| subjects affected / exposed                      | 4 / 366 (1.09%)      | 6 / 734 (0.82%)      | 2 / 368 (0.54%)      |
| occurrences (all)                                | 5                    | 7                    | 2                    |
| Headache                                         |                      |                      |                      |
| subjects affected / exposed                      | 10 / 366 (2.73%)     | 21 / 734 (2.86%)     | 11 / 368 (2.99%)     |
| occurrences (all)                                | 10                   | 23                   | 13                   |
| Blood and lymphatic system disorders             |                      |                      |                      |
| Anaemia                                          |                      |                      |                      |
| subjects affected / exposed                      | 0 / 366 (0.00%)      | 4 / 734 (0.54%)      | 4 / 368 (1.09%)      |
| occurrences (all)                                | 0                    | 4                    | 4                    |
| Ear and labyrinth disorders                      |                      |                      |                      |
| Vertigo                                          |                      |                      |                      |
| subjects affected / exposed                      | 4 / 366 (1.09%)      | 8 / 734 (1.09%)      | 4 / 368 (1.09%)      |
| occurrences (all)                                | 4                    | 9                    | 5                    |
| Eye disorders                                    |                      |                      |                      |

|                                                          |                  |                  |                  |
|----------------------------------------------------------|------------------|------------------|------------------|
| Cataract - Study Eye                                     |                  |                  |                  |
| subjects affected / exposed                              | 5 / 366 (1.37%)  | 12 / 734 (1.63%) | 7 / 368 (1.90%)  |
| occurrences (all)                                        | 5                | 12               | 7                |
| Eye pain - Study Eye                                     |                  |                  |                  |
| subjects affected / exposed                              | 17 / 366 (4.64%) | 30 / 734 (4.09%) | 13 / 368 (3.53%) |
| occurrences (all)                                        | 20               | 37               | 17               |
| Detachment of retinal pigment epithelium - Study Eye     |                  |                  |                  |
| subjects affected / exposed                              | 0 / 366 (0.00%)  | 4 / 734 (0.54%)  | 4 / 368 (1.09%)  |
| occurrences (all)                                        | 0                | 4                | 4                |
| Conjunctival haemorrhage - Study Eye                     |                  |                  |                  |
| subjects affected / exposed                              | 23 / 366 (6.28%) | 36 / 734 (4.90%) | 13 / 368 (3.53%) |
| occurrences (all)                                        | 26               | 46               | 20               |
| Foreign body sensation in eyes - Study Eye               |                  |                  |                  |
| subjects affected / exposed                              | 5 / 366 (1.37%)  | 13 / 734 (1.77%) | 8 / 368 (2.17%)  |
| occurrences (all)                                        | 5                | 16               | 11               |
| Macular oedema - Study Eye                               |                  |                  |                  |
| subjects affected / exposed                              | 3 / 366 (0.82%)  | 7 / 734 (0.95%)  | 4 / 368 (1.09%)  |
| occurrences (all)                                        | 4                | 8                | 4                |
| Neovascular age-related macular degeneration - Study Eye |                  |                  |                  |
| subjects affected / exposed                              | 3 / 366 (0.82%)  | 7 / 734 (0.95%)  | 4 / 368 (1.09%)  |
| occurrences (all)                                        | 4                | 8                | 4                |
| Posterior capsule opacification - Study Eye              |                  |                  |                  |
| subjects affected / exposed                              | 3 / 366 (0.82%)  | 8 / 734 (1.09%)  | 5 / 368 (1.36%)  |
| occurrences (all)                                        | 3                | 8                | 5                |
| Dry eye - Study Eye                                      |                  |                  |                  |
| subjects affected / exposed                              | 8 / 366 (2.19%)  | 26 / 734 (3.54%) | 18 / 368 (4.89%) |
| occurrences (all)                                        | 8                | 26               | 18               |
| Vitreous floaters - Study Eye                            |                  |                  |                  |
| subjects affected / exposed                              | 14 / 366 (3.83%) | 20 / 734 (2.72%) | 6 / 368 (1.63%)  |
| occurrences (all)                                        | 16               | 23               | 7                |
| Vitreous detachment - Study Eye                          |                  |                  |                  |
| subjects affected / exposed                              | 11 / 366 (3.01%) | 14 / 734 (1.91%) | 3 / 368 (0.82%)  |
| occurrences (all)                                        | 12               | 15               | 3                |
| Visual acuity reduced - Study Eye                        |                  |                  |                  |

|                                             |                  |                  |                  |
|---------------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed                 | 18 / 366 (4.92%) | 37 / 734 (5.04%) | 19 / 368 (5.16%) |
| occurrences (all)                           | 20               | 43               | 23               |
| Vision blurred - Study Eye                  |                  |                  |                  |
| subjects affected / exposed                 | 4 / 366 (1.09%)  | 5 / 734 (0.68%)  | 1 / 368 (0.27%)  |
| occurrences (all)                           | 4                | 5                | 1                |
| Subretinal fluid - Study Eye                |                  |                  |                  |
| subjects affected / exposed                 | 5 / 366 (1.37%)  | 16 / 734 (2.18%) | 11 / 368 (2.99%) |
| occurrences (all)                           | 5                | 20               | 15               |
| Subretinal fibrosis - Study Eye             |                  |                  |                  |
| subjects affected / exposed                 | 4 / 366 (1.09%)  | 4 / 734 (0.54%)  | 0 / 368 (0.00%)  |
| occurrences (all)                           | 4                | 4                | 0                |
| Retinal pigment epithelial tear - Study Eye |                  |                  |                  |
| subjects affected / exposed                 | 5 / 366 (1.37%)  | 9 / 734 (1.23%)  | 4 / 368 (1.09%)  |
| occurrences (all)                           | 5                | 9                | 4                |
| Retinal oedema - Study Eye                  |                  |                  |                  |
| subjects affected / exposed                 | 1 / 366 (0.27%)  | 5 / 734 (0.68%)  | 4 / 368 (1.09%)  |
| occurrences (all)                           | 1                | 6                | 5                |
| Retinal haemorrhage - Study Eye             |                  |                  |                  |
| subjects affected / exposed                 | 4 / 366 (1.09%)  | 11 / 734 (1.50%) | 7 / 368 (1.90%)  |
| occurrences (all)                           | 4                | 11               | 7                |
| Conjunctival haemorrhage - Fellow Eye       |                  |                  |                  |
| subjects affected / exposed                 | 3 / 366 (0.82%)  | 7 / 734 (0.95%)  | 4 / 368 (1.09%)  |
| occurrences (all)                           | 4                | 8                | 4                |
| Choroidal neovascularisation - Fellow Eye   |                  |                  |                  |
| subjects affected / exposed                 | 5 / 366 (1.37%)  | 12 / 734 (1.63%) | 7 / 368 (1.90%)  |
| occurrences (all)                           | 5                | 12               | 7                |
| Vitreous detachment - Fellow Eye            |                  |                  |                  |
| subjects affected / exposed                 | 5 / 366 (1.37%)  | 6 / 734 (0.82%)  | 1 / 368 (0.27%)  |
| occurrences (all)                           | 5                | 6                | 1                |
| Visual acuity reduced - Fellow Eye          |                  |                  |                  |
| subjects affected / exposed                 | 4 / 366 (1.09%)  | 8 / 734 (1.09%)  | 4 / 368 (1.09%)  |
| occurrences (all)                           | 7                | 11               | 4                |
| Retinal depigmentation - Study Eye          |                  |                  |                  |

|                                                                                                                          |                        |                        |                        |
|--------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                                                         | 1 / 366 (0.27%)<br>1   | 5 / 734 (0.68%)<br>5   | 4 / 368 (1.09%)<br>4   |
| Neovascular age-related macular<br>degeneration - Fellow Eye<br>subjects affected / exposed<br>occurrences (all)         | 22 / 366 (6.01%)<br>22 | 39 / 734 (5.31%)<br>40 | 17 / 368 (4.62%)<br>18 |
| Lacrimation increased - Fellow Eye<br>subjects affected / exposed<br>occurrences (all)                                   | 1 / 366 (0.27%)<br>1   | 5 / 734 (0.68%)<br>5   | 4 / 368 (1.09%)<br>4   |
| Eye pruritus - Study Eye<br>subjects affected / exposed<br>occurrences (all)                                             | 4 / 366 (1.09%)<br>4   | 5 / 734 (0.68%)<br>5   | 1 / 368 (0.27%)<br>1   |
| Eye pain - Fellow Eye<br>subjects affected / exposed<br>occurrences (all)                                                | 2 / 366 (0.55%)<br>2   | 6 / 734 (0.82%)<br>6   | 4 / 368 (1.09%)<br>4   |
| Dry eye - Fellow Eye<br>subjects affected / exposed<br>occurrences (all)                                                 | 6 / 366 (1.64%)<br>6   | 22 / 734 (3.00%)<br>22 | 16 / 368 (4.35%)<br>16 |
| Gastrointestinal disorders<br>Vomiting<br>subjects affected / exposed<br>occurrences (all)                               | 5 / 366 (1.37%)<br>5   | 5 / 734 (0.68%)<br>5   | 0 / 368 (0.00%)<br>0   |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                                            | 7 / 366 (1.91%)<br>7   | 9 / 734 (1.23%)<br>9   | 2 / 368 (0.54%)<br>2   |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                                                         | 4 / 366 (1.09%)<br>4   | 4 / 734 (0.54%)<br>4   | 0 / 368 (0.00%)<br>0   |
| Musculoskeletal and connective tissue<br>disorders<br>Osteoarthritis<br>subjects affected / exposed<br>occurrences (all) | 6 / 366 (1.64%)<br>6   | 8 / 734 (1.09%)<br>8   | 2 / 368 (0.54%)<br>2   |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                            | 8 / 366 (2.19%)<br>8   | 16 / 734 (2.18%)<br>17 | 8 / 368 (2.17%)<br>9   |
| Infections and infestations                                                                                              |                        |                        |                        |

|                                    |                  |                  |                  |
|------------------------------------|------------------|------------------|------------------|
| COVID-19                           |                  |                  |                  |
| subjects affected / exposed        | 9 / 366 (2.46%)  | 25 / 734 (3.41%) | 16 / 368 (4.35%) |
| occurrences (all)                  | 9                | 25               | 16               |
| Nasopharyngitis                    |                  |                  |                  |
| subjects affected / exposed        | 12 / 366 (3.28%) | 23 / 734 (3.13%) | 11 / 368 (2.99%) |
| occurrences (all)                  | 15               | 29               | 14               |
| Hordeolum - Study Eye              |                  |                  |                  |
| subjects affected / exposed        | 4 / 366 (1.09%)  | 6 / 734 (0.82%)  | 2 / 368 (0.54%)  |
| occurrences (all)                  | 4                | 6                | 2                |
| Cystitis                           |                  |                  |                  |
| subjects affected / exposed        | 3 / 366 (0.82%)  | 8 / 734 (1.09%)  | 5 / 368 (1.36%)  |
| occurrences (all)                  | 4                | 16               | 12               |
| Urinary tract infection            |                  |                  |                  |
| subjects affected / exposed        | 11 / 366 (3.01%) | 21 / 734 (2.86%) | 10 / 368 (2.72%) |
| occurrences (all)                  | 15               | 29               | 14               |
| Conjunctivitis - Fellow Eye        |                  |                  |                  |
| subjects affected / exposed        | 4 / 366 (1.09%)  | 8 / 734 (1.09%)  | 4 / 368 (1.09%)  |
| occurrences (all)                  | 4                | 8                | 4                |
| Conjunctivitis - Study Eye         |                  |                  |                  |
| subjects affected / exposed        | 5 / 366 (1.37%)  | 10 / 734 (1.36%) | 5 / 368 (1.36%)  |
| occurrences (all)                  | 6                | 12               | 6                |
| Metabolism and nutrition disorders |                  |                  |                  |
| Hyperuricaemia                     |                  |                  |                  |
| subjects affected / exposed        | 1 / 366 (0.27%)  | 5 / 734 (0.68%)  | 4 / 368 (1.09%)  |
| occurrences (all)                  | 1                | 5                | 4                |
| Hypercholesterolaemia              |                  |                  |                  |
| subjects affected / exposed        | 4 / 366 (1.09%)  | 10 / 734 (1.36%) | 6 / 368 (1.63%)  |
| occurrences (all)                  | 4                | 10               | 6                |
| Diabetes mellitus                  |                  |                  |                  |
| subjects affected / exposed        | 4 / 366 (1.09%)  | 5 / 734 (0.68%)  | 1 / 368 (0.27%)  |
| occurrences (all)                  | 4                | 5                | 1                |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 02 June 2020      | To provide clarification and guidance on safety assessments in accordance to the USM regarding the post-marketing reports with brolocizumab (Beovu ®) in the treatment of nAMD, which were identified as retinal vasculitis (RV) and/or retinal vascular occlusion (RO), typically in the presence of IOI, that may result in severe vision loss. In addition, the amendment included the modifications due to COVID-19 pandemic.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 13 August 2021    | <p>To provide clarification and guidance on the early discontinuation of study treatment that was required for those subjects who were currently on q4w dosing beyond the first 3 monthly loading doses ("loading phase") or would need q4w dosing beyond the "loading phase" based on the investigator's assessment. This was as per the USM dated 27-May-2021 (based on CTH258AUS04 (MERLIN) Year 1 FIR indicating a higher frequency of IOI including RV, and RO in brolocizumab 6 mg q4w when compared to aflibercept 2 mg q4w (IOI: 9.3% vs 4.5% of which RV: 0.8% vs 0.0%; RO: 2.0% vs 0.0%, respectively).</p> <p>To provide clarification and guidance on the early discontinuation of study treatment that was required for those subjects with RV and RO events. This was as per the USM dated 10-Aug-2021 (based on the results of the mechanistic study BASICHR0049 which identified a causal link with an immune-mediated mechanism of the previously identified risk of RV and/or RO, typically in the presence of IOI).</p> <p>To update safety sections throughout the protocol including updates to the Risks and Benefits section and the creation of a new section under Safety Monitoring which consolidated all risk mitigation information into one section of the protocol.</p> |
| 23 September 2021 | To include information on the gender imbalance in the reported rates of IOI-related adverse events following brolocizumab treatment.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |

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:

