



## Clinical trial results:

### A 12-Month, 2-Arm, Randomized, Double-Masked, Multicenter Phase III Study Assessing the Efficacy and Safety of Brolucizumab every 4 weeks versus Aflibercept every 4 weeks in Adult Patients with Visual Impairment due to Diabetic Macular Edema (KINGFISHER)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-001004-37 |
| Trial protocol           | SK HU          |
| Global end of trial date | 24 March 2021  |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1            |
| This version publication date  | 08 April 2022 |
| First version publication date | 08 April 2022 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRTH258B2305 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03917472 |
| 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                       | 16 November 2021 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 24 March 2021    |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective for this study was to demonstrate that brolocizumab is non-inferior to aflibercept with respect to the change in visual acuity (VA) from baseline compared to Week 52 summarized below along with their respective endpoints.

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                          | 17 July 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 | Hungary: 51        |
| Country: Number of subjects enrolled | Israel: 27         |
| Country: Number of subjects enrolled | Slovakia: 47       |
| Country: Number of subjects enrolled | United States: 392 |
| Worldwide total number of subjects   | 517                |
| EEA total number of subjects         | 98                 |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23          | 0 |

|                           |     |
|---------------------------|-----|
| months)                   |     |
| Children (2-11 years)     | 0   |
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 323 |
| From 65 to 84 years       | 191 |
| 85 years and over         | 3   |

## Subject disposition

### Recruitment

Recruitment details:

Study centers (no. of sites): Hungary (5), Israel (5), Slovakia (7), United States (78).

Approximately, 495 subjects were planned to be randomized. Overall, 517 subjects were randomized either to brolocizumab 6 mg q4w arm (n=346) or aflibercept 2 mg q4w arm (n=171).

### Pre-assignment

Screening details:

The study included a screening period of up to 2 wks to assess eligibility, followed by a double-masked treatment period (Day 1 to Wk 48). For all subjects, the last study assessment was performed at the Wk 52/end of study (EOS) visit. All subjects had study visits q4w through Wk 52. The primary analysis was performed at the EOS visit (Wk 52).

### 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 6mg q4w |

Arm description:

Brolucizumab 6 mg/0.05 mL every 4 weeks.

|                                        |                        |
|----------------------------------------|------------------------|
| 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:

6 mg/0.05 mL

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | Aflibercept 2mg q4w |
|------------------|---------------------|

Arm description:

Aflibercept 2mg/0.05 mL every 4 weeks

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

Dosage and administration details:

2 mg/0.05 mL

| <b>Number of subjects in period 1</b> | <b>Brolucizumab 6mg<br/>q4w</b> | <b>Aflibercept 2mg q4w</b> |
|---------------------------------------|---------------------------------|----------------------------|
| Started                               | 346                             | 171                        |
| Completed                             | 311                             | 156                        |
| Not completed                         | 35                              | 15                         |
| Adverse event, serious fatal          | 7                               | 5                          |
| Consent withdrawn by subject          | 11                              | 4                          |
| Physician decision                    | 4                               | -                          |
| Adverse event, non-fatal              | 3                               | 1                          |
| Lost to follow-up                     | 10                              | 5                          |

## Baseline characteristics

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Brolucizumab 6mg q4w |
|-----------------------|----------------------|

Reporting group description:

Brolucizumab 6 mg/0.05 mL every 4 weeks.

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Aflibercept 2mg q4w |
|-----------------------|---------------------|

Reporting group description:

Aflibercept 2mg/0.05 mL every 4 weeks

| Reporting group values                        | Brolucizumab 6mg q4w | Aflibercept 2mg q4w | Total |
|-----------------------------------------------|----------------------|---------------------|-------|
| Number of subjects                            | 346                  | 171                 | 517   |
| Age Categorical<br>Units: participants        |                      |                     |       |
| <=18 years                                    | 0                    | 0                   | 0     |
| Between 18 and 65 years                       | 208                  | 115                 | 323   |
| >=65 years                                    | 138                  | 56                  | 194   |
| Age Continuous<br>Units: years                |                      |                     |       |
| arithmetic mean                               | 60.9                 | 60.2                |       |
| standard deviation                            | ± 10.59              | ± 9.31              | -     |
| Sex: Female, Male<br>Units: participants      |                      |                     |       |
| Female                                        | 152                  | 66                  | 218   |
| Male                                          | 194                  | 105                 | 299   |
| Race/Ethnicity, Customized<br>Units: Subjects |                      |                     |       |
| White                                         | 288                  | 145                 | 433   |
| Black or African American                     | 40                   | 15                  | 55    |
| Asian                                         | 14                   | 7                   | 21    |
| Native Hawaiian or Other Pacific Islander     | 1                    | 0                   | 1     |
| American Indian or Alaska Native              | 0                    | 1                   | 1     |
| Unknown                                       | 1                    | 3                   | 4     |
| More than one race                            | 2                    | 0                   | 2     |

## End points

### End points reporting groups

|                                                                          |                      |
|--------------------------------------------------------------------------|----------------------|
| Reporting group title                                                    | Brolucizumab 6mg q4w |
| Reporting group description:<br>Brolucizumab 6 mg/0.05 mL every 4 weeks. |                      |
| Reporting group title                                                    | Aflibercept 2mg q4w  |
| Reporting group description:<br>Aflibercept 2mg/0.05 mL every 4 weeks    |                      |
| Subject analysis set title                                               | Brolucizumab 6mg q4w |
| Subject analysis set type                                                | Full analysis        |
| Subject analysis set description:<br>Brolucizumab 6mg q4w                |                      |
| Subject analysis set title                                               | Aflibercept 2mg q4w  |
| Subject analysis set type                                                | Full analysis        |
| Subject analysis set description:<br>Aflibercept 2mg q4w                 |                      |

### Primary: Change from baseline in best-corrected visual acuity (BCVA) at Week 52

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Change from baseline in best-corrected visual acuity (BCVA) at Week 52 |
| End point description:<br>BCVA will be assessed using Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity testing charts.<br><br>Visual function of the study eye was assessed using the ETDRS protocol. Participants with a BCVA ETDRS letter score of 73 to 23 (per the inclusion criteria) (approximate Snellen equivalent of 20/40 to 20/320) in the study eye were included.<br><br>Min and max possible scores are 0-100 respectively. A higher score represents better functioning.<br><br>Last observation carried forward (LOCF) was used for the imputation of missing values. |                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Primary                                                                |
| End point timeframe:<br>Baseline, Week 52                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                        |

| End point values                             | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|----------------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                           | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed                  | 346                     | 171                    |  |  |
| Units: Scores on a scale                     |                         |                        |  |  |
| least squares mean (confidence interval 95%) | 12.2 (11.2 to 13.2)     | 11.0 (9.6 to 12.4)     |  |  |

### Statistical analyses

|                            |                                              |
|----------------------------|----------------------------------------------|
| Statistical analysis title | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups          | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 517                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           |                            |
| P-value                                 | = 0.099                    |
| Method                                  | ANOVA                      |
| Parameter estimate                      | LS mean difference         |
| Point estimate                          | 1.1                        |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | -0.6                       |
| upper limit                             | 2.9                        |
| Variability estimate                    | Standard error of the mean |
| Dispersion value                        | 0.89                       |

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups                       | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis | 517                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| P-value                                 | < 0.001                                      |
| Method                                  | ANOVA                                        |

### Secondary: Change from baseline in central subfield thickness (CSFT) at each post-baseline visit

|                                                                                                                                                         |                                                                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|
| End point title                                                                                                                                         | Change from baseline in central subfield thickness (CSFT) at each post-baseline visit |
| End point description:<br>Central Subfield Thickness assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. |                                                                                       |
| End point type                                                                                                                                          | Secondary                                                                             |
| End point timeframe:<br>Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52                                                                       |                                                                                       |

| End point values                             | Brolucizumab<br>6mg q4w   | Aflibercept<br>2mg q4w    |  |  |
|----------------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type                           | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed                  | 346                       | 171                       |  |  |
| Units: µm                                    |                           |                           |  |  |
| least squares mean (confidence interval 95%) |                           |                           |  |  |
| Week 4                                       | -146.9 (-157.9 to -136.0) | -119.5 (-135.1 to -103.9) |  |  |
| Week 8                                       | -174.4 (-185.3 to -163.4) | -144.1 (-159.7 to -128.5) |  |  |



|         |                           |                           |  |  |
|---------|---------------------------|---------------------------|--|--|
| Week 12 | -191.3 (-201.8 to -180.8) | -156.7 (-171.7 to -141.8) |  |  |
| Week 16 | -200.5 (-211.0 to -189.9) | -162.4 (-177.4 to -147.4) |  |  |
| Week 20 | -209.5 (-219.6 to -199.4) | -168.7 (-183.1 to -154.2) |  |  |
| Week 24 | -217.5 (-227.3 to -207.6) | -178.8 (-192.8 to -164.7) |  |  |
| Week 28 | -222.4 (-232.5 to -212.4) | -183.6 (-197.8 to -169.3) |  |  |
| Week 32 | -227.2 (-237.2 to -217.1) | -185.9 (-200.2 to -171.6) |  |  |
| Week 36 | -229.7 (-240.1 to -219.3) | -186.7 (-201.5 to -172.0) |  |  |
| Week 40 | -233.6 (-243.7 to -223.6) | -188.4 (-202.6 to -174.1) |  |  |
| Week 44 | -237.5 (-247.4 to -227.5) | -188.1 (-202.3 to -173.9) |  |  |
| Week 48 | -237.7 (-247.7 to -227.6) | -192.0 (-206.4 to -177.7) |  |  |
| Week 52 | -237.8 (-247.9 to -227.7) | -196.5 (-210.8 to -182.1) |  |  |

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups                       | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis | 517                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| P-value                                 | < 0.001                                      |
| Method                                  | ANOVA                                        |
| Parameter estimate                      | LS mean difference                           |
| Point estimate                          | -41.4                                        |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -58.9                                        |
| upper limit                             | -23.8                                        |
| Variability estimate                    | Standard error of the mean                   |
| Dispersion value                        | 8.94                                         |

### Secondary: Number of participants with fluid-free macula in the study eye at each post-baseline visit

|                        |                                                                                                                                                                               |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title        | Number of participants with fluid-free macula in the study eye at each post-baseline visit                                                                                    |
| End point description: |                                                                                                                                                                               |
|                        | Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) status in the central subfield: proportion of subjects with simultaneous absence of SRF and IRF in the study eye by visit |
| End point type         | Secondary                                                                                                                                                                     |

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

| End point values            | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|-----------------------------|-------------------------|------------------------|--|--|
| Subject group type          | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed | 346                     | 171                    |  |  |
| Units: Participants         |                         |                        |  |  |
| Week 4                      | 23                      | 4                      |  |  |
| Week 8                      | 31                      | 4                      |  |  |
| Week 12                     | 38                      | 10                     |  |  |
| Week 16                     | 48                      | 11                     |  |  |
| Week 20                     | 54                      | 9                      |  |  |
| Week 24                     | 84                      | 19                     |  |  |
| Week 28                     | 65                      | 13                     |  |  |
| Week 32                     | 76                      | 17                     |  |  |
| Week 36                     | 91                      | 21                     |  |  |
| Week 40                     | 96                      | 23                     |  |  |
| Week 44                     | 96                      | 20                     |  |  |
| week 48                     | 92                      | 23                     |  |  |
| Week 52                     | 144                     | 38                     |  |  |

### Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| Statistical analysis title              | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups                       | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis | 517                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| P-value                                 | < 0.001                                      |
| Method                                  | Clopper-Pearson exact method.                |
| Parameter estimate                      | Difference - %                               |
| Point estimate                          | 20                                           |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | 12.5                                         |
| upper limit                             | 28.6                                         |

### Secondary: Number of participants with absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) at each post-baseline visit for the study eye

|                 |                                                                                                                                   |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of participants with absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) at each post-baseline visit for the study eye |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------|

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center.

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

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

| End point values            | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|-----------------------------|-------------------------|------------------------|--|--|
| Subject group type          | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed | 346                     | 171                    |  |  |
| Units: Participants         |                         |                        |  |  |
| Week 4                      | 61                      | 9                      |  |  |
| Week 8                      | 93                      | 24                     |  |  |
| Week 12                     | 124                     | 33                     |  |  |
| Week 16                     | 147                     | 42                     |  |  |
| Week 20                     | 167                     | 47                     |  |  |
| Week 24                     | 177                     | 52                     |  |  |
| Week 28                     | 186                     | 57                     |  |  |
| Week 32                     | 195                     | 62                     |  |  |
| Week 36                     | 206                     | 63                     |  |  |
| Week 40                     | 211                     | 65                     |  |  |
| Week 44                     | 216                     | 69                     |  |  |
| Week 48                     | 222                     | 68                     |  |  |
| Week 52                     | 229                     | 71                     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to first fluid-free macula - Time-to-first absence of Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) in the study eye

|                 |                                                                                                                                 |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to first fluid-free macula - Time-to-first absence of Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) in the study eye |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------|

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. Fluid status assessments after start of alternative DME treatment in the study eye are censored. Time to first fluid-free macula analysis is based on the subset of subjects with fluid present at baseline and at least one post-baseline assessment. Time (week) was calculated by (study day / 7). Events and censoring after 52 weeks were included in week 52 row.

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

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

| <b>End point values</b>                          | <b>Brolucizumab<br/>6mg q4w</b> | <b>Aflibercept<br/>2mg q4w</b> |  |  |
|--------------------------------------------------|---------------------------------|--------------------------------|--|--|
| Subject group type                               | Reporting group                 | Reporting group                |  |  |
| Number of subjects analysed                      | 344                             | 170                            |  |  |
| Units: Participants                              |                                 |                                |  |  |
| N w/ absence of SRF/IRF at Wk 0<br>(n=344,170)   | 0                               | 0                              |  |  |
| N w/ absence of SRF/IRF at Wk 4<br>(n=344,170)   | 6                               | 1                              |  |  |
| N w/ absence of SRF/IRF at Wk 8<br>(n=335,168)   | 18                              | 3                              |  |  |
| N w/ absence of SRF/IRF at Wk 12<br>(n=314, 165) | 13                              | 2                              |  |  |
| N w/ absence of SRF/IRF at Wk 16<br>(n=297, 161) | 17                              | 4                              |  |  |
| N w/ absence of SRF/IRF at Wk 20<br>(n=277, 156) | 8                               | 6                              |  |  |
| N w/ absence of SRF/IRF at Wk 24<br>(n=265,150)  | 16                              | 2                              |  |  |
| N w/ absence of SRF/IRF at Wk 28<br>(n=246,146)  | 18                              | 7                              |  |  |
| N w/ absence of SRF/IRF at Wk 32<br>(n=224,139)  | 3                               | 1                              |  |  |
| N w/ absence of SRF/IRF at Wk 36<br>(n=220,138)  | 8                               | 2                              |  |  |
| N w/ absence of SRF/IRF at Wk 40<br>(n=211, 134) | 16                              | 4                              |  |  |
| N w/ absence of SRF/IRF at Wk 44 (194,<br>129)   | 11                              | 2                              |  |  |
| N w/ absence of SRF/IRF at Wk 48<br>(n=181, 125) | 3                               | 0                              |  |  |
| N w/ absence of SRF/IRF at Wk 52<br>(n=177, 122) | 30                              | 12                             |  |  |
| N censored at Week 0 (n=344, 170)                | 0                               | 0                              |  |  |
| N censored at Week 4 (n=344, 170)                | 3                               | 1                              |  |  |
| N censored at Week 8 (n=335,168)                 | 3                               | 0                              |  |  |
| N censored at Week 12 (n=314, 165)               | 4                               | 2                              |  |  |
| N censored at Week 16 (n=297, 161)               | 3                               | 1                              |  |  |
| N censored at Week 20 (n=277, 156)               | 4                               | 0                              |  |  |
| N censored at Week 24 (n=265, 150)               | 3                               | 2                              |  |  |
| N censored at Week 28 (n=246, 146)               | 4                               | 0                              |  |  |
| N censored at Week 32 (n=224,139)                | 1                               | 0                              |  |  |
| N censored at Week 36 (220, 138)                 | 1                               | 2                              |  |  |
| N censored at Week 40 (n=211,134)                | 1                               | 1                              |  |  |
| N censored at Week 44 (n=194,129)                | 2                               | 2                              |  |  |
| N censored at Week 48 (n=181, 125)               | 1                               | 3                              |  |  |
| N censored at Week 52 (n=177, 122)               | 147                             | 110                            |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to first fluid-free macula - Time-to-first absence of Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) in the study eye - Kaplan-Meier analysis

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Time to first fluid-free macula - Time-to-first absence of Subretinal Fluid (SRF) and Intraretinal Fluid (IRF) in the study eye - Kaplan-Meier analysis |
| End point description:<br>Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. Fluid status assessments after start of alternative DME treatment in the study eye are censored. Time to first fluid-free macula analysis is based on the subset of subjects with fluid present at baseline and at least one post-baseline assessment. Time (week) was calculated by (study day / 7). Events and censoring after 52 weeks were included in week 52 row. |                                                                                                                                                         |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Secondary                                                                                                                                               |
| End point timeframe:<br>Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                         |

| End point values                                                             | Brolucizumab<br>6mg q4w   | Aflibercept<br>2mg q4w    |  |  |
|------------------------------------------------------------------------------|---------------------------|---------------------------|--|--|
| Subject group type                                                           | Reporting group           | Reporting group           |  |  |
| Number of subjects analysed                                                  | 344                       | 170                       |  |  |
| Units: Probability of absence of SRF/IRF<br>number (confidence interval 95%) |                           |                           |  |  |
| Prob. of absence of SRF/IRF at Wk 4<br>(n=344,170)                           | 0.018 (0.007<br>to 0.036) | 0.006 (0.001<br>to 0.030) |  |  |
| Prob. of absence of SRF/IRF at Wk 8<br>(n=335,168)                           | 0.071 (0.047<br>to 0.101) | 0.024 (0.008<br>to 0.056) |  |  |
| Prob. of absence of SRF/IRF at Wk 12<br>(n=314, 165)                         | 0.109 (0.079<br>to 0.145) | 0.036 (0.015<br>to 0.072) |  |  |
| Prob. of absence of SRF/IRF at Wk 16<br>(n=297, 161)                         | 0.161 (0.124<br>to 0.202) | 0.060 (0.030<br>to 0.103) |  |  |
| Prob. of absence of SRF/IRF at Wk 20<br>(n=277, 156)                         | 0.185 (0.145<br>to 0.228) | 0.096 (0.057<br>to 0.146) |  |  |
| Prob. of absence of SRF/IRF at Wk 24<br>(n=265,150)                          | 0.234 (0.190<br>to 0.281) | 0.108 (0.067<br>to 0.161) |  |  |
| Prob. of absence of SRF/IRF at Wk 28<br>(n=246,146)                          | 0.291 (0.243<br>to 0.341) | 0.151 (0.101<br>to 0.210) |  |  |
| Prob. of absence of SRF/IRF at Wk 32<br>(n=224,139)                          | 0.300 (0.252<br>to 0.351) | 0.157 (0.106<br>to 0.217) |  |  |
| Prob. of absence of SRF/IRF at Wk 36<br>(n=220,138)                          | 0.326 (0.275<br>to 0.377) | 0.169 (0.116<br>to 0.230) |  |  |
| Prob. of absence of SRF/IRF at Wk 40<br>(n=211, 134)                         | 0.377 (0.324<br>to 0.430) | 0.194 (0.137<br>to 0.258) |  |  |
| Prob. of absence of SRF/IRF at Wk 44<br>(194, 129)                           | 0.412 (0.358<br>to 0.466) | 0.206 (0.148<br>to 0.271) |  |  |
| Prob. of absence of SRF/IRF at Wk 48<br>(n=181, 125)                         | 0.422 (0.368<br>to 0.476) | 0.206 (0.148<br>to 0.271) |  |  |
| Prob. of absence of SRF/IRF at Wk 52<br>(n=177, 122)                         | 0.653 (0.540<br>to 0.745) | 0.328 (0.234<br>to 0.426) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to first absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) in the study eye at each post-baseline visit

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Time to first absence of Diabetic Macular Edema (DME) (CSFT |
|-----------------|-------------------------------------------------------------|

## End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. CSFT assessments after start of alternative DME treatment in the study eye are censored. Time to first absence of DME based on subjects with valid baseline and at least one post-baseline CSFT assessment. Time (week) was calculated by (study day / 7). Events and censoring after 52 weeks were included in week 52 row.

## End point type

Secondary

## End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

| End point values                                      | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|-------------------------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                                    | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed                           | 346                     | 171                    |  |  |
| Units: Participants                                   |                         |                        |  |  |
| N w/ Prob. of absence of DME at Wk 0<br>(n=346,171)   | 0                       | 0                      |  |  |
| N w/ Prob. of absence of DME at Wk 4<br>(n=346,171)   | 14                      | 1                      |  |  |
| N w/ Prob. of absence of DME at Wk 8<br>(n=329,169)   | 54                      | 12                     |  |  |
| N w/ Prob. of absence of DME at Wk 12<br>(n=272, 157) | 32                      | 13                     |  |  |
| N w/ Prob. of absence of DME at Wk 16<br>(n=239, 142) | 33                      | 11                     |  |  |
| N w/ Prob. of absence of DME at Wk 20<br>(n=204, 130) | 26                      | 10                     |  |  |
| N w/ Prob. of absence of DME at Wk 24<br>(n=174,120)  | 12                      | 4                      |  |  |
| N w/ Prob. of absence of DME at Wk 28<br>(n=161,115)  | 13                      | 7                      |  |  |
| N w/ Prob. of absence of DME at Wk 32<br>(n=146,107)  | 9                       | 5                      |  |  |
| N w/ Prob. of absence of DME at Wk 36<br>(n=135,102)  | 10                      | 2                      |  |  |
| N w/ Prob. of absence of DME at Wk 40<br>(n=125, 98)  | 7                       | 1                      |  |  |
| N w/ Prob. of absence of DME at Wk 44<br>(117, 96)    | 11                      | 2                      |  |  |
| N w/ Prob. of absence of DME at Wk 48<br>(n=106, 92)  | 6                       | 3                      |  |  |
| N w/ Prob. of absence of DME at Wk 52<br>(n=99, 88)   | 13                      | 4                      |  |  |
| Number censored at Week 0<br>(n=346,171)              | 0                       | 0                      |  |  |
| Number censored at Week 4<br>(n=346,171)              | 3                       | 1                      |  |  |
| Number censored at Week 8<br>(n=329,169)              | 3                       | 0                      |  |  |
| Number censored at Week 12 (n=272,<br>157)            | 1                       | 2                      |  |  |
| Number censored at Week 16 (n=239,<br>142)            | 2                       | 1                      |  |  |
| Number censored at Week 20 (n=204,<br>130)            | 4                       | 0                      |  |  |

|                                        |    |    |  |  |
|----------------------------------------|----|----|--|--|
| Number censored at Week 24 (n=174,120) | 1  | 1  |  |  |
| Number censored at Week 28 (n=161,115) | 2  | 1  |  |  |
| Number censored at Week 32 (n=146,107) | 2  | 0  |  |  |
| Number censored at Week 36 (n=135,102) | 0  | 2  |  |  |
| Number censored at Week 40 (n=125, 98) | 1  | 1  |  |  |
| Number censored at Week 44 (117, 96)   | 0  | 2  |  |  |
| Number censored at Week 48 (n=106, 92) | 1  | 1  |  |  |
| Number censored at Week 52 (n=99, 88)  | 86 | 84 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to first absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) in the study eye at each post-baseline visit - Kaplan-Meier analysis

|                 |                                                                                                                                            |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Time to first absence of Diabetic Macular Edema (DME) (CSFT < 280 µm) in the study eye at each post-baseline visit - Kaplan-Meier analysis |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Central Subfield Thickness Assessed by Spectral domain optical coherence tomography (SD-OCT) from the central reading center. CSFT assessments after start of alternative DME treatment in the study eye are censored. Time to first absence of DME based on subjects with valid baseline and at least one post-baseline CSFT assessment. Time (week) was calculated by (study day / 7). Events and censoring after 52 weeks were included in week 52 row.

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

End point timeframe:

Baselinet, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

| End point values                                | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|-------------------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                              | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed                     | 346                     | 171                    |  |  |
| Units: Probability of absence of DME            |                         |                        |  |  |
| number (confidence interval 95%)                |                         |                        |  |  |
| Prob. of absence of DME at Week 4 (n=346,171)   | 0.041 (0.023 to 0.066)  | 0.006 (0.001 to 0.030) |  |  |
| Prob. of absence of DME at Week 8 (n=329,169)   | 0.199 (0.158 to 0.243)  | 0.076 (0.043 to 0.123) |  |  |
| Prob. of absence of DME at Week 12 (n=272, 157) | 0.293 (0.246 to 0.342)  | 0.153 (0.104 to 0.212) |  |  |
| Prob. of absence of DME at Week 16 (n=239, 142) | 0.391 (0.339 to 0.443)  | 0.219 (0.160 to 0.284) |  |  |
| Prob. of absence of DME at Week 20 (n=204, 130) | 0.470 (0.416 to 0.522)  | 0.279 (0.213 to 0.348) |  |  |
| Prob. of absence of DME at Week 24 (n=174,120)  | 0.506 (0.452 to 0.559)  | 0.303 (0.235 to 0.374) |  |  |

|                                                |                        |                        |  |  |
|------------------------------------------------|------------------------|------------------------|--|--|
| Prob. of absence of DME at Week 28 (n=161,115) | 0.547 (0.491 to 0.598) | 0.346 (0.274 to 0.418) |  |  |
| Prob. of absence of DME at Week 32 (n=146,107) | 0.575 (0.520 to 0.626) | 0.376 (0.303 to 0.450) |  |  |
| Prob. of absence of DME at Week 36 (n=135,102) | 0.606 (0.551 to 0.657) | 0.389 (0.314 to 0.462) |  |  |
| Prob. of absence of DME at Week 40 (n=125, 98) | 0.628 (0.574 to 0.678) | 0.395 (0.320 to 0.468) |  |  |
| Prob. of absence of DME at Week 44 (117, 96)   | 0.663 (0.609 to 0.712) | 0.408 (0.332 to 0.482) |  |  |
| Prob. of absence of DME at Week 48 (n=106, 92) | 0.682 (0.629 to 0.730) | 0.427 (0.351 to 0.501) |  |  |
| Prob. of absence of DME at Week 52 (n=99, 88)  | 0.866 (0.302 to 0.983) | 0.516 (0.357 to 0.654) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Best Corrected Visual Acuity (letters read): Change from baseline in best-corrected visual acuity (BCVA) at each post-baseline visit for the study eye

|                 |                                                                                                                                                        |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Best Corrected Visual Acuity (letters read): Change from baseline in best-corrected visual acuity (BCVA) at each post-baseline visit for the study eye |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

Visual function of the study eye was assessed using the ETDRS protocol. Participants with a BCVA ETDRS letter score of 73 to 23 (per the inclusion criteria) (approximate Snellen equivalent of 20/40 to 20/320) in the study eye were included.

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

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

End point timeframe:

Baseline, Weeks 4,8,12,16,20,24,28,32,36,40,44,48 and 52

| End point values                             | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|----------------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                           | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed                  | 346                     | 171                    |  |  |
| Units: scores on a scale                     |                         |                        |  |  |
| least squares mean (confidence interval 95%) |                         |                        |  |  |
| Week 4                                       | 5.7 (5.1 to 6.4)        | 5.4 (4.5 to 6.4)       |  |  |
| Week 8                                       | 7.7 (6.9 to 8.5)        | 7.4 (6.4 to 8.5)       |  |  |
| Week 12                                      | 9.1 (8.3 to 9.9)        | 8.0 (6.9 to 9.1)       |  |  |
| Week 16                                      | 9.6 (8.8 to 10.4)       | 8.5 (7.3 to 9.7)       |  |  |
| Week 20                                      | 10.2 (9.3 to 11.1)      | 9.2 (7.9 to 10.5)      |  |  |
| Week 24                                      | 10.7 (9.8 to 11.6)      | 9.6 (8.3 to 10.9)      |  |  |



|         |                     |                    |  |  |
|---------|---------------------|--------------------|--|--|
| Week 28 | 10.9 (10.0 to 11.8) | 10.7 (9.3 to 12.0) |  |  |
| Week 32 | 11.5 (10.6 to 12.5) | 10.5 (9.2 to 11.9) |  |  |
| Week 36 | 11.6 (10.6 to 12.6) | 10.8 (9.4 to 12.2) |  |  |
| Week 40 | 11.7 (10.7 to 12.6) | 10.7 (9.4 to 12.1) |  |  |
| Week 44 | 12.0 (11.0 to 13.0) | 10.6 (9.2 to 12.0) |  |  |
| Week 48 | 12.2 (11.2 to 13.2) | 10.7 (9.3 to 12.1) |  |  |
| Week 52 | 12.2 (11.2 to 13.2) | 11.0 (9.6 to 12.4) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Gain in best-corrected visual acuity (BCVA) (letters read): number (%) of subjects who gained $\geq 5$ , 10, or 15 letters in BCVA from baseline or reached BCVA $\geq 84$ letters in the study eye at Week 52

|                 |                                                                                                                                                                                                                |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Gain in best-corrected visual acuity (BCVA) (letters read): number (%) of subjects who gained $\geq 5$ , 10, or 15 letters in BCVA from baseline or reached BCVA $\geq 84$ letters in the study eye at Week 52 |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

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

Visual function of the study eye was assessed using the ETDRS protocol. Participants with a BCVA ETDRS letter score of 73 to 23 (per the inclusion criteria) (approximate Snellen equivalent of 20/40 to 20/320) in the study eye were included.

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

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

End point timeframe:

Baseline, Week 52

| End point values                                                 | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|------------------------------------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                                               | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed                                      | 346                     | 171                    |  |  |
| Units: Participants                                              |                         |                        |  |  |
| $\geq 5$ letters gain from b/l or BCVA $\geq 84$ letters at Wk52 | 286                     | 127                    |  |  |
| $\geq 10$ letters gain from b/l or BCVA $\geq 84$ letters at W52 | 211                     | 95                     |  |  |
| $\geq 15$ letters gain from b/l or BCVA $\geq 84$ letters at W52 | 151                     | 69                     |  |  |

## Statistical analyses

|                                                                          |                                              |
|--------------------------------------------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>                                        | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Statistical analysis description:                                        |                                              |
| $\geq 5$ letters gain from baseline or BCVA $\geq 84$ letters at Week 52 |                                              |
| Comparison groups                                                        | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis                                  | 517                                          |
| Analysis specification                                                   | Pre-specified                                |
| Analysis type                                                            |                                              |
| Method                                                                   | Clopper-Pearson exact method                 |
| Parameter estimate                                                       | Difference - %                               |
| Point estimate                                                           | 9.3                                          |
| Confidence interval                                                      |                                              |
| level                                                                    | 95 %                                         |
| sides                                                                    | 2-sided                                      |
| lower limit                                                              | 1.7                                          |
| upper limit                                                              | 17                                           |

|                                                                           |                                              |
|---------------------------------------------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>                                         | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Statistical analysis description:                                         |                                              |
| $\geq 10$ letters gain from baseline or BCVA $\geq 84$ letters at Week 52 |                                              |
| Comparison groups                                                         | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis                                   | 517                                          |
| Analysis specification                                                    | Pre-specified                                |
| Analysis type                                                             |                                              |
| Method                                                                    | Clopper-Pearson exact method                 |
| Parameter estimate                                                        | Difference - %                               |
| Point estimate                                                            | 7.7                                          |
| Confidence interval                                                       |                                              |
| level                                                                     | 95 %                                         |
| sides                                                                     | 2-sided                                      |
| lower limit                                                               | -1.5                                         |
| upper limit                                                               | 17                                           |

|                                                                           |                                              |
|---------------------------------------------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>                                         | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Statistical analysis description:                                         |                                              |
| $\geq 15$ letters gain from baseline or BCVA $\geq 84$ letters at Week 52 |                                              |
| Comparison groups                                                         | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis                                   | 517                                          |
| Analysis specification                                                    | Pre-specified                                |
| Analysis type                                                             |                                              |
| Method                                                                    | Clopper-Pearson exact method                 |
| Parameter estimate                                                        | Difference - %                               |
| Point estimate                                                            | 5.5                                          |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -2.7    |
| upper limit         | 14.3    |

**Secondary: Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic retinopathy severity scale (DRSS): proportion of subjects with  $\geq 2$ -step improvement from baseline in the DRSS score at each assessment visit for the study eye**

|                 |                                                                                                                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic retinopathy severity scale (DRSS): proportion of subjects with $\geq 2$ -step improvement from baseline in the DRSS score at each assessment visit for the study eye |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**End point description:**

The Diabetic Retinopathy Disease Severity Scale measures the 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative.

Severity of Diabetic retinopathy was evaluated using the ETDRS DRSS score assessed by the Central Reading Center based on color fundus photography images in the study eye. When the ETDRS-DR severities were evaluable, they were categorized on the original scale with scores varying from 10 (DR absent) to 85 (very advanced PDR). All DRSS values were then converted into a 12-level scale, allowing the derivation of the  $\geq 2$ -step and  $\geq 3$ -step change from baseline for each post-baseline assessment".

A lower score represents better functioning.

Subjects who had full/partial panretinal photocoagulation or local photocoagulation for new vessel (DRSS score 60) at any visit were excluded.

DRSS scores after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

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

**End point timeframe:**

Baseline, Weeks 12, 24 and 52

| End point values            | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|-----------------------------|-------------------------|------------------------|--|--|
| Subject group type          | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed | 221                     | 118                    |  |  |
| Units: Participants         |                         |                        |  |  |
| Week 12                     | 56                      | 21                     |  |  |
| Week 24                     | 82                      | 38                     |  |  |
| Week 52                     | 95                      | 45                     |  |  |

**Statistical analyses**

|                            |                                              |
|----------------------------|----------------------------------------------|
| Statistical analysis title | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups          | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |

|                                         |                              |
|-----------------------------------------|------------------------------|
| Number of subjects included in analysis | 339                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           |                              |
| Method                                  | Clopper-Pearson exact method |
| Parameter estimate                      | Difference - %               |
| Point estimate                          | 8.3                          |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.2                          |
| upper limit                             | 16.5                         |

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups                       | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis | 339                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| P-value                                 | = 0.002 <sup>[1]</sup>                       |
| Method                                  | Clopper-Pearson exact method                 |
| Parameter estimate                      | Difference - %                               |
| Point estimate                          | 6                                            |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -3.9                                         |
| upper limit                             | 16.1                                         |

Notes:

[1] - (10% margin) (1-sided)

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups                       | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis | 339                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| Method                                  | Clopper-Pearson exact method                 |
| Parameter estimate                      | Difference - %                               |
| Point estimate                          | 6                                            |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -3                                           |
| upper limit                             | 14.9                                         |

**Secondary: Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic retinopathy severity scale (DRSS): proportion of subjects with  $\geq 3$ -step improvement from baseline in the DRSS score at each assessment visit for the study**

## eye

|                 |                                                                                                                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Early Treatment Diabetic Retinopathy Study (ETDRS) Diabetic retinopathy severity scale (DRSS): proportion of subjects with $\geq 3$ -step improvement from baseline in the DRSS score at each assessment visit for the study eye |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

The Diabetic Retinopathy Disease Severity Scale measures the 5 levels of diabetic retinopathy - none, mild, moderate, severe, and proliferative.

Severity of Diabetic retinopathy was evaluated using the ETDRS DRSS score assessed by the Central Reading Center based on color fundus photography images in the study eye. When the ETDRS-DR severities were evaluable, they were categorized on the original scale with scores varying from 10 (DR absent) to 85 (very advanced PDR). All DRSS values were then converted into a 12-level scale, allowing the derivation of the  $\geq 2$ -step and  $\geq 3$ -step change from baseline for each post-baseline assessment".

A lower score represents better functioning.

Subjects who had full/partial panretinal photocoagulation or local photocoagulation for new vessel (DRSS score 60) at any visit were excluded.

DRSS scores after start of alternative DME treatment in the study eye are censored and replaced by the last value prior to start of this alternative treatment.

|                      |                               |
|----------------------|-------------------------------|
| End point type       | Secondary                     |
| End point timeframe: | Baseline, Weeks 12, 24 and 52 |

| End point values            | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|-----------------------------|-------------------------|------------------------|--|--|
| Subject group type          | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed | 221                     | 118                    |  |  |
| Units: Participants         |                         |                        |  |  |
| Week 12                     | 18                      | 8                      |  |  |
| Week 24                     | 33                      | 16                     |  |  |
| Week 52                     | 40                      | 18                     |  |  |

## Statistical analyses

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| Statistical analysis title              | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups                       | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis | 339                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| Method                                  | Clopper-Pearson exact method                 |
| Parameter estimate                      | Difference - %                               |
| Point estimate                          | 2.4                                          |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -3                                           |
| upper limit                             | 7.7                                          |

|                                         |                                              |
|-----------------------------------------|----------------------------------------------|
| <b>Statistical analysis title</b>       | Brolucizumab 6mg q4w vs. Aflibercept 2mg q4w |
| Comparison groups                       | Brolucizumab 6mg q4w v Aflibercept 2mg q4w   |
| Number of subjects included in analysis | 339                                          |
| Analysis specification                  | Pre-specified                                |
| Analysis type                           |                                              |
| Method                                  | Clopper-Pearson exact method                 |
| Parameter estimate                      | Difference - %                               |
| Point estimate                          | 3.9                                          |
| Confidence interval                     |                                              |
| level                                   | 95 %                                         |
| sides                                   | 2-sided                                      |
| lower limit                             | -2                                           |
| upper limit                             | 9.8                                          |

### Secondary: Anti-Drug Antibody (ADA): frequency distribution of pre-existing ADA status in the Brolucizumab arm

|                        |                                                                                                     |
|------------------------|-----------------------------------------------------------------------------------------------------|
| End point title        | Anti-Drug Antibody (ADA): frequency distribution of pre-existing ADA status in the Brolucizumab arm |
| End point description: |                                                                                                     |
| End point type         | Secondary                                                                                           |
| End point timeframe:   |                                                                                                     |
| Baseline               |                                                                                                     |

| End point values            | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|-----------------------------|-------------------------|------------------------|--|--|
| Subject group type          | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed | 342                     | 0 <sup>[2]</sup>       |  |  |
| Units: Participants         |                         |                        |  |  |
| Negative                    | 112                     |                        |  |  |
| Positive                    | 230                     |                        |  |  |

Notes:

[2] - Endpoint only defined for the Brolucizumab 6mg q4w arm

### Statistical analyses

No statistical analyses for this end point

### Post-hoc: Ocular AEs (greater than or equal to 2% in any treatment arm) by preferred term in the study eye

|                 |                                                                                                  |
|-----------------|--------------------------------------------------------------------------------------------------|
| End point title | Ocular AEs (greater than or equal to 2% in any treatment arm) by preferred term in the study eye |
|-----------------|--------------------------------------------------------------------------------------------------|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 52 weeks.

| End point values                        | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
|-----------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                      | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed             | 346                     | 171                    |  |  |
| Units: Participants                     |                         |                        |  |  |
| Number of subjects with at least one AE | 105                     | 59                     |  |  |
| Vitreous detachment                     | 10                      | 7                      |  |  |
| Cataract                                | 9                       | 6                      |  |  |
| Conjunctival haemorrhage                | 9                       | 7                      |  |  |
| Punctate keratitis                      | 9                       | 2                      |  |  |
| Uveitis                                 | 8                       | 1                      |  |  |
| Vitreous floaters                       | 8                       | 5                      |  |  |
| Dry eye                                 | 7                       | 4                      |  |  |
| Eye pain                                | 6                       | 5                      |  |  |
| Corneal abrasion                        | 0                       | 5                      |  |  |
| Diabetic retinal oedema                 | 0                       | 4                      |  |  |

## Statistical analyses

No statistical analyses for this end point

### Post-hoc: Number of subjects with non-ocular AEs (greater than or equal to 2% in any treatment arm)

|                 |                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------|
| End point title | Number of subjects with non-ocular AEs (greater than or equal to 2% in any treatment arm) |
|-----------------|-------------------------------------------------------------------------------------------|

End point description:

|                |          |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 52 weeks.

|                                         |                         |                        |  |  |
|-----------------------------------------|-------------------------|------------------------|--|--|
| <b>End point values</b>                 | Brolucizumab<br>6mg q4w | Aflibercept<br>2mg q4w |  |  |
| Subject group type                      | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed             | 346                     | 171                    |  |  |
| Units: Participants                     |                         |                        |  |  |
| Number of subjects with at least one AE | 209                     | 96                     |  |  |

### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 52 weeks.

Adverse event reporting additional description:

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

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

### Dictionary used

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

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

### Reporting groups

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

Reporting group description:

Brolucizumab 6mg

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

Reporting group description:

Overall

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

Reporting group description:

Aflibercept 2mg

| Serious adverse events                                              | Brolucizumab 6mg  | Overall            | Aflibercept 2mg   |
|---------------------------------------------------------------------|-------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                    |                   |
| subjects affected / exposed                                         | 74 / 346 (21.39%) | 110 / 517 (21.28%) | 36 / 171 (21.05%) |
| number of deaths (all causes)                                       | 7                 | 12                 | 5                 |
| number of deaths resulting from adverse events                      | 0                 | 0                  | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                    |                   |
| Adrenal adenoma                                                     |                   |                    |                   |
| subjects affected / exposed                                         | 1 / 346 (0.29%)   | 1 / 517 (0.19%)    | 0 / 171 (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             |
| Bladder cancer                                                      |                   |                    |                   |
| subjects affected / exposed                                         | 0 / 346 (0.00%)   | 1 / 517 (0.19%)    | 1 / 171 (0.58%)   |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1              | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 1              | 0 / 1             |
| Gastric neoplasm                                                    |                   |                    |                   |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Leukaemia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Extremity necrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 3 / 517 (0.58%) | 2 / 171 (1.17%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive emergency                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Hypertensive urgency                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Orthostatic hypotension                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 2 / 517 (0.39%) | 1 / 171 (0.58%) |
| 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                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral vascular disorder                    |                 |                 |                 |

|                                                      |                 |                 |                 |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Chest pain                                           |                 |                 |                 |
| subjects affected / exposed                          | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Generalised oedema                                   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Oedema peripheral                                    |                 |                 |                 |
| subjects affected / exposed                          | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral swelling                                  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Sudden death                                         |                 |                 |                 |
| subjects affected / exposed                          | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                 |
| Acute pulmonary oedema                               |                 |                 |                 |
| subjects affected / exposed                          | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Acute respiratory failure                            |                 |                 |                 |
| subjects affected / exposed                          | 1 / 346 (0.29%) | 2 / 517 (0.39%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Dyspnoea                                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Interstitial lung disease                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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                     | 1 / 346 (0.29%) | 2 / 517 (0.39%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Pulmonary oedema                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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 failure                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Investigations                                  |                 |                 |                 |
| Blood glucose increased                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| 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 potassium increased                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Troponin increased                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural                |                 |                 |                 |

|                                                 |                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|-----------------|--|
| complications                                   |                 |                 |                 |  |
| Anastomotic ulcer haemorrhage                   |                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Ankle fracture                                  |                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |  |
| Cataract operation complication - Fellow eye    |                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |  |
| Contusion                                       |                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |
| Forearm fracture                                |                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |  |
| Limb injury                                     |                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |  |
| Patella fracture                                |                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 346 (0.58%) | 2 / 517 (0.39%) | 0 / 171 (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           |  |
| Post-traumatic neck syndrome                    |                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Postoperative ileus                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 346 (0.58%) | 2 / 517 (0.39%) | 0 / 171 (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           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Acute left ventricular failure                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 2 / 517 (0.39%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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                     | 2 / 346 (0.58%) | 2 / 517 (0.39%) | 0 / 171 (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           |
| Atrioventricular block second degree            |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 3 / 346 (0.87%) | 4 / 517 (0.77%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           | 0 / 1           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 4 / 346 (1.16%) | 4 / 517 (0.77%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiopulmonary failure                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 3 / 346 (0.87%) | 4 / 517 (0.77%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Left ventricular failure                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| 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                     | 3 / 346 (0.87%) | 4 / 517 (0.77%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |

|                                                 |                 |                  |                 |
|-------------------------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 2 / 346 (0.58%) | 3 / 517 (0.58%)  | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Nervous system disorders                        |                 |                  |                 |
| Cerebral haemorrhage                            |                 |                  |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%)  | 1 / 171 (0.58%) |
| 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                     | 6 / 346 (1.73%) | 12 / 517 (2.32%) | 6 / 171 (3.51%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 12           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1            | 0 / 0           |
| Epilepsy                                        |                 |                  |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%)  | 0 / 171 (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           |
| Ischaemic stroke                                |                 |                  |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 2 / 517 (0.39%)  | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Lacunar stroke                                  |                 |                  |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%)  | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Lumbar radiculopathy                            |                 |                  |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%)  | 0 / 171 (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           |
| Thrombotic stroke                               |                 |                  |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%)  | 1 / 171 (0.58%) |
| 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 / 346 (0.29%) | 2 / 517 (0.39%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |                 |
| <b>Anaemia</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 2 / 517 (0.39%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypochromic anaemia</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Iron deficiency anaemia</b>                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| <b>Ear and labyrinth disorders</b>              |                 |                 |                 |
| <b>Vertigo</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| <b>Eye disorders</b>                            |                 |                 |                 |
| <b>Cataract - Fellow eye</b>                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cataract subcapsular - Study eye</b>         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| <b>Diabetic retinopathy - Fellow eye</b>        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                                  |                 |                 |                 |
|------------------------------------------------------------------|-----------------|-----------------|-----------------|
| Retinal vasculitis - Study eye<br>subjects affected / exposed    | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to<br>treatment / all               | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Vitreous haemorrhage - Fellow eye<br>subjects affected / exposed | 2 / 346 (0.58%) | 2 / 517 (0.39%) | 0 / 171 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Vitreous haemorrhage - Study eye<br>subjects affected / exposed  | 2 / 346 (0.58%) | 2 / 517 (0.39%) | 0 / 171 (0.00%) |
| occurrences causally related to<br>treatment / all               | 1 / 2           | 1 / 2           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                                       |                 |                 |                 |
| Abdominal pain<br>subjects affected / exposed                    | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic gastroparesis<br>subjects affected / exposed            | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspepsia<br>subjects affected / exposed                         | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal perforation<br>subjects affected / exposed      | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to<br>treatment / all               | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting<br>subjects affected / exposed                          | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to<br>treatment / all               | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all                    | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                                          |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Liver disorder                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Diabetic foot                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic wound                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 4 / 346 (1.16%) | 5 / 517 (0.97%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 6           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic kidney disease                          |                 |                 |                 |
| subjects affected / exposed                     | 3 / 346 (0.87%) | 3 / 517 (0.58%) | 0 / 171 (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           |
| Hydronephrosis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Renal colic                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 346 (0.58%) | 2 / 517 (0.39%) | 0 / 171 (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           |
| Renal impairment                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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 mass                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Pathological fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Infections and infestations                     |                 |                 |                 |
| Abscess bacterial                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Abscess limb                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Bronchitis viral                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19                                        |                 |                 |                 |
| subjects affected / exposed                     | 8 / 346 (2.31%) | 9 / 517 (1.74%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 9           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 3           | 0 / 0           |
| COVID-19 pneumonia                              |                 |                 |                 |
| subjects affected / exposed                     | 4 / 346 (1.16%) | 4 / 517 (0.77%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 346 (0.87%) | 3 / 517 (0.58%) | 0 / 171 (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           |
| Chest wall abscess                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Cholecystitis infective                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cytomegalovirus infection                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Diabetic foot infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 3 / 517 (0.58%) | 2 / 171 (1.17%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic gangrene                               |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gangrene                                        |                 |                 |                 |
| subjects affected / exposed                     | 2 / 346 (0.58%) | 3 / 517 (0.58%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Kidney infection                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Lymphangitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteomyelitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 346 (0.87%) | 5 / 517 (0.97%) | 2 / 171 (1.17%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 346 (0.87%) | 5 / 517 (0.97%) | 2 / 171 (1.17%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| Sepsis                                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 346 (0.58%) | 3 / 517 (0.58%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Staphylococcal sepsis                           |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Subcutaneous abscess                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Wound infection staphylococcal                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Fluid retention                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (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           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 346 (0.00%) | 1 / 517 (0.19%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 2 / 517 (0.39%) | 1 / 171 (0.58%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 346 (0.29%) | 1 / 517 (0.19%) | 0 / 171 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | <b>Brolucizumab 6mg</b> | <b>Overall</b>     | <b>Aflibercept 2mg</b> |
|-------------------------------------------------------|-------------------------|--------------------|------------------------|
| Total subjects affected by non-serious adverse events |                         |                    |                        |
| subjects affected / exposed                           | 144 / 346 (41.62%)      | 236 / 517 (45.65%) | 92 / 171 (53.80%)      |
| Vascular disorders                                    |                         |                    |                        |
| Hypertension                                          |                         |                    |                        |
| subjects affected / exposed                           | 18 / 346 (5.20%)        | 31 / 517 (6.00%)   | 13 / 171 (7.60%)       |
| occurrences (all)                                     | 19                      | 32                 | 13                     |
| General disorders and administration site conditions  |                         |                    |                        |
| Oedema peripheral                                     |                         |                    |                        |
| subjects affected / exposed                           | 3 / 346 (0.87%)         | 7 / 517 (1.35%)    | 4 / 171 (2.34%)        |
| occurrences (all)                                     | 3                       | 7                  | 4                      |
| Pyrexia                                               |                         |                    |                        |
| subjects affected / exposed                           | 4 / 346 (1.16%)         | 8 / 517 (1.55%)    | 4 / 171 (2.34%)        |
| occurrences (all)                                     | 6                       | 10                 | 4                      |
| Respiratory, thoracic and mediastinal disorders       |                         |                    |                        |
| Cough                                                 |                         |                    |                        |
| subjects affected / exposed                           | 3 / 346 (0.87%)         | 12 / 517 (2.32%)   | 9 / 171 (5.26%)        |
| occurrences (all)                                     | 4                       | 13                 | 9                      |
| Investigations                                        |                         |                    |                        |
| Blood creatinine increased                            |                         |                    |                        |
| subjects affected / exposed                           | 4 / 346 (1.16%)         | 11 / 517 (2.13%)   | 7 / 171 (4.09%)        |
| occurrences (all)                                     | 4                       | 11                 | 7                      |
| Blood pressure increased                              |                         |                    |                        |
| subjects affected / exposed                           | 7 / 346 (2.02%)         | 12 / 517 (2.32%)   | 5 / 171 (2.92%)        |
| occurrences (all)                                     | 7                       | 12                 | 5                      |
| Injury, poisoning and procedural complications        |                         |                    |                        |
| Corneal abrasion - Study eye                          |                         |                    |                        |
| subjects affected / exposed                           | 0 / 346 (0.00%)         | 5 / 517 (0.97%)    | 5 / 171 (2.92%)        |
| occurrences (all)                                     | 0                       | 5                  | 5                      |
| Fall                                                  |                         |                    |                        |
| subjects affected / exposed                           | 9 / 346 (2.60%)         | 13 / 517 (2.51%)   | 4 / 171 (2.34%)        |
| occurrences (all)                                     | 10                      | 14                 | 4                      |
| Nervous system disorders                              |                         |                    |                        |



|                                                                                                     |                        |                        |                       |
|-----------------------------------------------------------------------------------------------------|------------------------|------------------------|-----------------------|
| Headache<br>subjects affected / exposed<br>occurrences (all)                                        | 3 / 346 (0.87%)<br>3   | 10 / 517 (1.93%)<br>11 | 7 / 171 (4.09%)<br>8  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all) | 8 / 346 (2.31%)<br>8   | 12 / 517 (2.32%)<br>12 | 4 / 171 (2.34%)<br>4  |
| Eye disorders<br>Cataract - Fellow eye<br>subjects affected / exposed<br>occurrences (all)          | 6 / 346 (1.73%)<br>6   | 10 / 517 (1.93%)<br>10 | 4 / 171 (2.34%)<br>4  |
| Cataract - Study eye<br>subjects affected / exposed<br>occurrences (all)                            | 9 / 346 (2.60%)<br>9   | 15 / 517 (2.90%)<br>15 | 6 / 171 (3.51%)<br>6  |
| Conjunctival haemorrhage - Fellow eye<br>subjects affected / exposed<br>occurrences (all)           | 4 / 346 (1.16%)<br>4   | 9 / 517 (1.74%)<br>10  | 5 / 171 (2.92%)<br>6  |
| Conjunctival haemorrhage - Study eye<br>subjects affected / exposed<br>occurrences (all)            | 9 / 346 (2.60%)<br>10  | 16 / 517 (3.09%)<br>20 | 7 / 171 (4.09%)<br>10 |
| Diabetic retinal oedema - Fellow eye<br>subjects affected / exposed<br>occurrences (all)            | 10 / 346 (2.89%)<br>10 | 17 / 517 (3.29%)<br>17 | 7 / 171 (4.09%)<br>7  |
| Diabetic retinal oedema - Study eye<br>subjects affected / exposed<br>occurrences (all)             | 0 / 346 (0.00%)<br>0   | 4 / 517 (0.77%)<br>4   | 4 / 171 (2.34%)<br>4  |
| Dry eye - Fellow eye<br>subjects affected / exposed<br>occurrences (all)                            | 6 / 346 (1.73%)<br>6   | 12 / 517 (2.32%)<br>12 | 6 / 171 (3.51%)<br>6  |
| Dry eye - Study eye<br>subjects affected / exposed<br>occurrences (all)                             | 7 / 346 (2.02%)<br>7   | 11 / 517 (2.13%)<br>11 | 4 / 171 (2.34%)<br>4  |
| Eye pain - Fellow eye<br>subjects affected / exposed<br>occurrences (all)                           | 3 / 346 (0.87%)<br>3   | 7 / 517 (1.35%)<br>7   | 4 / 171 (2.34%)<br>4  |
| Eye pain - Study eye                                                                                |                        |                        |                       |

|                                                                                                                  |                        |                        |                        |
|------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)                                                                 | 6 / 346 (1.73%)<br>6   | 11 / 517 (2.13%)<br>11 | 5 / 171 (2.92%)<br>5   |
| Punctate keratitis - Study eye<br>subjects affected / exposed<br>occurrences (all)                               | 9 / 346 (2.60%)<br>12  | 11 / 517 (2.13%)<br>15 | 2 / 171 (1.17%)<br>3   |
| Uveitis - Study eye<br>subjects affected / exposed<br>occurrences (all)                                          | 8 / 346 (2.31%)<br>9   | 9 / 517 (1.74%)<br>10  | 1 / 171 (0.58%)<br>1   |
| Vitreous detachment - Study eye<br>subjects affected / exposed<br>occurrences (all)                              | 10 / 346 (2.89%)<br>10 | 17 / 517 (3.29%)<br>17 | 7 / 171 (4.09%)<br>7   |
| Vitreous floaters - Study eye<br>subjects affected / exposed<br>occurrences (all)                                | 8 / 346 (2.31%)<br>8   | 13 / 517 (2.51%)<br>13 | 5 / 171 (2.92%)<br>5   |
| Vitreous haemorrhage - Fellow eye<br>subjects affected / exposed<br>occurrences (all)                            | 10 / 346 (2.89%)<br>11 | 14 / 517 (2.71%)<br>15 | 4 / 171 (2.34%)<br>4   |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                         | 3 / 346 (0.87%)<br>3   | 7 / 517 (1.35%)<br>8   | 4 / 171 (2.34%)<br>5   |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all)           | 8 / 346 (2.31%)<br>9   | 12 / 517 (2.32%)<br>13 | 4 / 171 (2.34%)<br>4   |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)                                       | 8 / 346 (2.31%)<br>9   | 12 / 517 (2.32%)<br>13 | 4 / 171 (2.34%)<br>4   |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 346 (0.87%)<br>3   | 7 / 517 (1.35%)<br>7   | 4 / 171 (2.34%)<br>4   |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all)                      | 11 / 346 (3.18%)<br>12 | 22 / 517 (4.26%)<br>23 | 11 / 171 (6.43%)<br>11 |

|                                    |                  |                  |                 |
|------------------------------------|------------------|------------------|-----------------|
| Cellulitis                         |                  |                  |                 |
| subjects affected / exposed        | 7 / 346 (2.02%)  | 11 / 517 (2.13%) | 4 / 171 (2.34%) |
| occurrences (all)                  | 8                | 12               | 4               |
| Influenza                          |                  |                  |                 |
| subjects affected / exposed        | 2 / 346 (0.58%)  | 6 / 517 (1.16%)  | 4 / 171 (2.34%) |
| occurrences (all)                  | 2                | 6                | 4               |
| Nasopharyngitis                    |                  |                  |                 |
| subjects affected / exposed        | 8 / 346 (2.31%)  | 14 / 517 (2.71%) | 6 / 171 (3.51%) |
| occurrences (all)                  | 8                | 14               | 6               |
| Urinary tract infection            |                  |                  |                 |
| subjects affected / exposed        | 11 / 346 (3.18%) | 13 / 517 (2.51%) | 2 / 171 (1.17%) |
| occurrences (all)                  | 12               | 14               | 2               |
| Metabolism and nutrition disorders |                  |                  |                 |
| Diabetes mellitus                  |                  |                  |                 |
| subjects affected / exposed        | 7 / 346 (2.02%)  | 7 / 517 (1.35%)  | 0 / 171 (0.00%) |
| occurrences (all)                  | 7                | 7                | 0               |
| Type 2 diabetes mellitus           |                  |                  |                 |
| subjects affected / exposed        | 5 / 346 (1.45%)  | 9 / 517 (1.74%)  | 4 / 171 (2.34%) |
| occurrences (all)                  | 5                | 9                | 4               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 08 June 2020 | The main purpose of this amendment was to provide clarification and guidance on safety assessments in accordance with the urgent safety measure regarding the post-marketing reports with brovacizumab (Beovu®) in the treatment of nAMD, which were identified as retinal vasculitis and/or retinal vascular occlusion, typically in the presence of IOI, that could result in severe vision loss. In addition, the amendment included the modifications due to COVID-19 pandemic. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

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: