



## Clinical trial results:

### A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Faricimab in Patients With Neovascular Age-Related Macular Degeneration (AVONELLE-X)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2020-004523-16                |
| Trial protocol           | FR PT DE AT DK HU PL NL IT BG |
| Global end of trial date | 03 September 2024             |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1              |
| This version publication date  | 23 October 2025 |
| First version publication date | 23 October 2025 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | GR42691 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04777201 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                                                                           |
|------------------------------|-----------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | F. Hoffmann-La Roche, Ltd.                                                                                |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, 4058                                                           |
| Public contact               | F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche, Ltd., F. Hoffmann-La Roche, Ltd., +41 616878333, global.trial_information@roche.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                       | 03 September 2024 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 03 September 2024 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 03 September 2024 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the main study was to evaluate the long-term ocular and systemic safety and tolerability of faricimab in all patients who enrolled in the long-term extension study. The primary objective of the substudy was to evaluate the impact of faricimab on corneal endothelial cell health, as assessed by specular microscopy.

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual.

Background therapy: -

Evidence for comparator: -

|                                                           |               |
|-----------------------------------------------------------|---------------|
| Actual start date of recruitment                          | 19 April 2021 |
| Long term follow-up planned                               | No            |
| Independent data monitoring committee (IDMC) involvement? | No            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 54          |
| Country: Number of subjects enrolled | Australia: 21          |
| Country: Number of subjects enrolled | Austria: 12            |
| Country: Number of subjects enrolled | Bulgaria: 5            |
| Country: Number of subjects enrolled | Brazil: 4              |
| Country: Number of subjects enrolled | Canada: 26             |
| Country: Number of subjects enrolled | Denmark: 7             |
| Country: Number of subjects enrolled | France: 18             |
| Country: Number of subjects enrolled | Germany: 10            |
| Country: Number of subjects enrolled | Hong Kong: 9           |
| Country: Number of subjects enrolled | Hungary: 42            |
| Country: Number of subjects enrolled | Israel: 22             |
| Country: Number of subjects enrolled | Italy: 13              |
| Country: Number of subjects enrolled | Japan: 98              |
| Country: Number of subjects enrolled | Korea, Republic of: 31 |
| Country: Number of subjects enrolled | Mexico: 3              |
| Country: Number of subjects enrolled | Netherlands: 4         |
| Country: Number of subjects enrolled | Poland: 61             |
| Country: Number of subjects enrolled | Portugal: 8            |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Russian Federation: 26 |
| Country: Number of subjects enrolled | Singapore: 1           |
| Country: Number of subjects enrolled | Spain: 47              |
| Country: Number of subjects enrolled | Switzerland: 1         |
| Country: Number of subjects enrolled | Taiwan: 17             |
| Country: Number of subjects enrolled | Türkiye: 18            |
| Country: Number of subjects enrolled | United Kingdom: 37     |
| Country: Number of subjects enrolled | United States: 434     |
| Worldwide total number of subjects   | 1029                   |
| EEA total number of subjects         | 227                    |

Notes:

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### Subjects enrolled per age group

|                                           |     |
|-------------------------------------------|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 78  |
| From 65 to 84 years                       | 746 |
| 85 years and over                         | 205 |

## Subject disposition

### Recruitment

Recruitment details:

A total of 1036 participants were enrolled in the main study, 7 of whom were excluded from analysis as an outcome of the GCP non-compliance audit finding, resulting in a final analysis set of 1029 participants. A subgroup of 117 also participated concurrently in the substudy.

### Pre-assignment

Screening details:

A total of 7 patients were not included in the analysis set prior to assignment. This was a precautionary measure following a Good Clinical Practice (GCP) non-compliance audit finding at a single clinical trial site for a different investigational product.

### Period 1

|                              |                             |
|------------------------------|-----------------------------|
| Period 1 title               | Main Study (overall period) |
| Is this the baseline period? | Yes                         |
| Allocation method            | Non-randomised - controlled |
| Blinding used                | Not blinded                 |

### Arms

|                              |                                                      |
|------------------------------|------------------------------------------------------|
| Are arms mutually exclusive? | Yes                                                  |
| <b>Arm title</b>             | Main Study Cohort A: Faricimab PTI (Prior Faricimab) |

Arm description:

This cohort included participants previously randomized to Arm A (faricimab up to every 16 weeks [Q16W]) in the parent studies [GR40306 (NCT03823287) or GR40844 (NCT03823300)]. In this long-term extension study, faricimab 6 mg was administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Faricimab              |
| Investigational medicinal product code | RO6867461              |
| Other name                             | VABYSMO®               |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravitreal use       |

Dosage and administration details:

Faricimab 6 mg will be administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                  |                                                        |
|------------------|--------------------------------------------------------|
| <b>Arm title</b> | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) |
|------------------|--------------------------------------------------------|

Arm description:

This cohort included participants previously randomized to Arm B (aflibercept 2 mg Q8W) in the parent studies [GR40306 (NCT03823287) or GR40844 (NCT03823300)]. In this long-term extension study, faricimab 6 mg was administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Faricimab              |
| Investigational medicinal product code | RO6867461              |
| Other name                             | VABYSMO®               |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Intravitreal use       |

Dosage and administration details:

Faricimab 6 mg will be administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

| <b>Number of subjects in period 1</b>     | <b>Main Study Cohort<br/>A: Faricimab PTI<br/>(Prior Faricimab)</b> | <b>Main Study Cohort<br/>B: Faricimab PTI<br/>(Prior Aflibercept)</b> |
|-------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------|
| Started                                   | 524                                                                 | 505                                                                   |
| Safety-Evaluable Population               | 520                                                                 | 505                                                                   |
| Completed                                 | 453                                                                 | 415                                                                   |
| Not completed                             | 71                                                                  | 90                                                                    |
| Adverse event, serious fatal              | 13                                                                  | 27                                                                    |
| Consent withdrawn by subject              | 19                                                                  | 27                                                                    |
| Physician decision                        | 8                                                                   | 10                                                                    |
| Adverse event, non-fatal                  | 8                                                                   | 8                                                                     |
| Lost to follow-up                         | 9                                                                   | 4                                                                     |
| Subject missed the safety follow-up visit | 9                                                                   | 10                                                                    |
| Reason not specified                      | 3                                                                   | 3                                                                     |
| Lack of efficacy                          | 1                                                                   | 1                                                                     |
| Protocol deviation                        | 1                                                                   | -                                                                     |

## Baseline characteristics

### Reporting groups

|                       |                                                      |
|-----------------------|------------------------------------------------------|
| Reporting group title | Main Study Cohort A: Faricimab PTI (Prior Faricimab) |
|-----------------------|------------------------------------------------------|

Reporting group description:

This cohort included participants previously randomized to Arm A (faricimab up to every 16 weeks [Q16W]) in the parent studies [GR40306 (NCT03823287) or GR40844 (NCT03823300)]. In this long-term extension study, faricimab 6 mg was administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                       |                                                        |
|-----------------------|--------------------------------------------------------|
| Reporting group title | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) |
|-----------------------|--------------------------------------------------------|

Reporting group description:

This cohort included participants previously randomized to Arm B (aflibercept 2 mg Q8W) in the parent studies [GR40306 (NCT03823287) or GR40844 (NCT03823300)]. In this long-term extension study, faricimab 6 mg was administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

| Reporting group values                             | Main Study Cohort A: Faricimab PTI (Prior Faricimab) | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) | Total |
|----------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|-------|
| Number of subjects                                 | 524                                                  | 505                                                    | 1029  |
| Age categorical                                    |                                                      |                                                        |       |
| Units: Subjects                                    |                                                      |                                                        |       |
| In utero                                           | 0                                                    | 0                                                      | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0                                                    | 0                                                      | 0     |
| Newborns (0-27 days)                               | 0                                                    | 0                                                      | 0     |
| Infants and toddlers (28 days-23 months)           | 0                                                    | 0                                                      | 0     |
| Children (2-11 years)                              | 0                                                    | 0                                                      | 0     |
| Adolescents (12-17 years)                          | 0                                                    | 0                                                      | 0     |
| Adults (18-64 years)                               | 41                                                   | 37                                                     | 78    |
| From 65-84 years                                   | 398                                                  | 348                                                    | 746   |
| 85 years and over                                  | 85                                                   | 120                                                    | 205   |
| Age Continuous                                     |                                                      |                                                        |       |
| Units: Years                                       |                                                      |                                                        |       |
| arithmetic mean                                    | 76.4                                                 | 77.7                                                   | -     |
| standard deviation                                 | ± 8.2                                                | ± 8.8                                                  | -     |
| Sex: Female, Male                                  |                                                      |                                                        |       |
| Units: Participants                                |                                                      |                                                        |       |
| Female                                             | 308                                                  | 291                                                    | 599   |
| Male                                               | 216                                                  | 214                                                    | 430   |
| Ethnicity (NIH/OMB)                                |                                                      |                                                        |       |
| Units: Subjects                                    |                                                      |                                                        |       |
| Hispanic or Latino                                 | 50                                                   | 53                                                     | 103   |
| Not Hispanic or Latino                             | 463                                                  | 445                                                    | 908   |
| Unknown or Not Reported                            | 11                                                   | 7                                                      | 18    |
| Race (NIH/OMB)                                     |                                                      |                                                        |       |
| Units: Subjects                                    |                                                      |                                                        |       |
| American Indian or Alaska Native                   | 2                                                    | 2                                                      | 4     |
| Asian                                              | 76                                                   | 83                                                     | 159   |
| Native Hawaiian or Other Pacific Islander          | 0                                                    | 0                                                      | 0     |

|                           |     |     |     |
|---------------------------|-----|-----|-----|
| Black or African American | 1   | 5   | 6   |
| White                     | 433 | 402 | 835 |
| More than one race        | 0   | 1   | 1   |
| Unknown or Not Reported   | 12  | 12  | 24  |

## Subject analysis sets

|                            |                                          |
|----------------------------|------------------------------------------|
| Subject analysis set title | Substudy: Faricimab PTI in the Study Eye |
| Subject analysis set type  | Modified intention-to-treat              |

### Subject analysis set description:

This analysis group represents the results for the substudy participants' study eyes. Participants from the main long-term extension study who also consented to participate in this substudy received faricimab 6 mg by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                            |                             |
|----------------------------|-----------------------------|
| Subject analysis set title | Substudy: Fellow Eye        |
| Subject analysis set type  | Modified intention-to-treat |

### Subject analysis set description:

This analysis group represents the results for the substudy participants' fellow (non-study) eyes. The fellow eyes of enrolled participants in the substudy were used as a comparator. At the discretion of the principal investigator, fellow eyes were allowed to be treated with standard of care anti-VEGF therapy (if needed) according to region-specific prescribing information. Administration of the following therapies to the fellow eye were prohibited during the substudy: faricimab, brolucizumab, bevacizumab, and Port Delivery System implantation.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Substudy: Faricimab PTI |
| Subject analysis set type  | Safety analysis         |

### Subject analysis set description:

Participants from the main long-term extension study who also consented to participate in this substudy received faricimab 6 mg by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study. The fellow eyes of enrolled participants in the substudy were used as a comparator. At the discretion of the principal investigator, fellow eyes were allowed to be treated with standard of care anti-VEGF therapy (if needed) according to region-specific prescribing information. Administration of the following therapies to the fellow eye were prohibited during the substudy: faricimab, brolucizumab, bevacizumab, and Port Delivery System implantation.

| Reporting group values                                                                                                                                                                                                                                    | Substudy: Faricimab PTI in the Study Eye | Substudy: Fellow Eye | Substudy: Faricimab PTI |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|----------------------|-------------------------|
| Number of subjects                                                                                                                                                                                                                                        | 113                                      | 113                  | 113                     |
| Age categorical<br>Units: Subjects                                                                                                                                                                                                                        |                                          |                      |                         |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |                                          |                      |                         |
| Age Continuous<br>Units: Years                                                                                                                                                                                                                            |                                          |                      |                         |
| arithmetic mean                                                                                                                                                                                                                                           |                                          |                      | 75.6                    |
| standard deviation                                                                                                                                                                                                                                        | ±                                        | ±                    | ± 8.1                   |

|                                           |  |  |     |
|-------------------------------------------|--|--|-----|
| Sex: Female, Male                         |  |  |     |
| Units: Participants                       |  |  |     |
| Female                                    |  |  | 61  |
| Male                                      |  |  | 52  |
| Ethnicity (NIH/OMB)                       |  |  |     |
| Units: Subjects                           |  |  |     |
| Hispanic or Latino                        |  |  | 23  |
| Not Hispanic or Latino                    |  |  | 90  |
| Unknown or Not Reported                   |  |  | 0   |
| Race (NIH/OMB)                            |  |  |     |
| Units: Subjects                           |  |  |     |
| American Indian or Alaska Native          |  |  | 0   |
| Asian                                     |  |  | 0   |
| Native Hawaiian or Other Pacific Islander |  |  | 0   |
| Black or African American                 |  |  | 1   |
| White                                     |  |  | 112 |
| More than one race                        |  |  | 0   |
| Unknown or Not Reported                   |  |  | 0   |

## End points

### End points reporting groups

|                       |                                                      |
|-----------------------|------------------------------------------------------|
| Reporting group title | Main Study Cohort A: Faricimab PTI (Prior Faricimab) |
|-----------------------|------------------------------------------------------|

#### Reporting group description:

This cohort included participants previously randomized to Arm A (faricimab up to every 16 weeks [Q16W]) in the parent studies [GR40306 (NCT03823287) or GR40844 (NCT03823300)]. In this long-term extension study, faricimab 6 mg was administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                       |                                                        |
|-----------------------|--------------------------------------------------------|
| Reporting group title | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) |
|-----------------------|--------------------------------------------------------|

#### Reporting group description:

This cohort included participants previously randomized to Arm B (aflibercept 2 mg Q8W) in the parent studies [GR40306 (NCT03823287) or GR40844 (NCT03823300)]. In this long-term extension study, faricimab 6 mg was administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                            |                                          |
|----------------------------|------------------------------------------|
| Subject analysis set title | Substudy: Faricimab PTI in the Study Eye |
|----------------------------|------------------------------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

#### Subject analysis set description:

This analysis group represents the results for the substudy participants' study eyes. Participants from the main long-term extension study who also consented to participate in this substudy received faricimab 6 mg by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                            |                      |
|----------------------------|----------------------|
| Subject analysis set title | Substudy: Fellow Eye |
|----------------------------|----------------------|

|                           |                             |
|---------------------------|-----------------------------|
| Subject analysis set type | Modified intention-to-treat |
|---------------------------|-----------------------------|

#### Subject analysis set description:

This analysis group represents the results for the substudy participants' fellow (non-study) eyes. The fellow eyes of enrolled participants in the substudy were used as a comparator. At the discretion of the principal investigator, fellow eyes were allowed to be treated with standard of care anti-VEGF therapy (if needed) according to region-specific prescribing information. Administration of the following therapies to the fellow eye were prohibited during the substudy: faricimab, brolucizumab, bevacizumab, and Port Delivery System implantation.

|                            |                         |
|----------------------------|-------------------------|
| Subject analysis set title | Substudy: Faricimab PTI |
|----------------------------|-------------------------|

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

#### Subject analysis set description:

Participants from the main long-term extension study who also consented to participate in this substudy received faricimab 6 mg by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study. The fellow eyes of enrolled participants in the substudy were used as a comparator. At the discretion of the principal investigator, fellow eyes were allowed to be treated with standard of care anti-VEGF therapy (if needed) according to region-specific prescribing information. Administration of the following therapies to the fellow eye were prohibited during the substudy: faricimab, brolucizumab, bevacizumab, and Port Delivery System implantation.

### Primary: Incidence and Severity of Ocular Adverse Events in the Study Eye, with Severity Determined According to Adverse Event Severity Grading Scale

|                 |                                                                                                                                                             |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Incidence and Severity of Ocular Adverse Events in the Study Eye, with Severity Determined According to Adverse Event Severity Grading Scale <sup>[1]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|

#### End point description:

This is an analysis of participants with at least one ocular adverse event (AE) that occurred in the study eye. Investigators sought information on AEs at each contact with the participants. All AEs were recorded and the investigator made an assessment of the seriousness, severity (e.g., mild, moderate, or severe intensity), and causality for each AE. AEs of special interest (AESI) included the following: Sight-threatening AEs that cause a drop in visual acuity (VA) score  $\geq 30$  letters lasting more than 1 hour, are associated with severe intraocular inflammation (IOI), or require surgical or medical intervention to prevent permanent loss of sight; suspected transmission of an infectious agent by the study drug; and, cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.

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

End point timeframe:

From the date of first administration of faricimab through 28 days after the end of study (up to 2 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned. The adverse events were summarized descriptively.

| End point values                                    | Main Study Cohort A: Faricimab PTI (Prior Faricimab) | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) | Substudy: Faricimab PTI |  |
|-----------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|-------------------------|--|
| Subject group type                                  | Reporting group                                      | Reporting group                                        | Subject analysis set    |  |
| Number of subjects analysed                         | 520                                                  | 505                                                    | 113                     |  |
| Units: participants                                 |                                                      |                                                        |                         |  |
| Any Adverse Event (AE), Any Severity                | 188                                                  | 207                                                    | 16                      |  |
| AEs by Severity: Mild                               | 114                                                  | 106                                                    | 11                      |  |
| AEs by Severity: Moderate                           | 58                                                   | 75                                                     | 4                       |  |
| AEs by Severity: Severe                             | 13                                                   | 23                                                     | 1                       |  |
| AEs by Severity: Missing                            | 3                                                    | 3                                                      | 0                       |  |
| Serious Adverse Event (SAE)                         | 18                                                   | 27                                                     | 1                       |  |
| AE Leading to Withdrawal from Study Treatment       | 4                                                    | 5                                                      | 0                       |  |
| Treatment-related AE                                | 8                                                    | 12                                                     | 2                       |  |
| Treatment-related SAE                               | 1                                                    | 3                                                      | 1                       |  |
| Any AE of Special Interest (AESI)                   | 15                                                   | 21                                                     | 1                       |  |
| AESI: Drop in Visual Acuity Score $\geq 30$ Letters | 11                                                   | 16                                                     | 1                       |  |
| AESI: Associated with Severe IOI                    | 1                                                    | 2                                                      | 0                       |  |
| AESI: Intervention Req. to Prev. Perm. Vision Loss  | 3                                                    | 3                                                      | 0                       |  |
| AESI: Suspect. Transm. of Infectious Agent by Drug  | 0                                                    | 0                                                      | 0                       |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Incidence of Ocular Adverse Events in the Fellow Eye

|                 |                                                                     |
|-----------------|---------------------------------------------------------------------|
| End point title | Incidence of Ocular Adverse Events in the Fellow Eye <sup>[2]</sup> |
|-----------------|---------------------------------------------------------------------|

End point description:

This is an analysis of participants with at least one ocular adverse event (AE) that occurred in the study eye. Investigators sought information on AEs at each contact with the participants. All AEs were recorded and the investigator made an assessment of the seriousness, severity, and causality for each AE. AEs of special interest (AESI) included the following: Sight-threatening AEs that cause a drop in visual acuity (VA) score  $\geq 30$  letters lasting more than 1 hour, are associated with severe intraocular inflammation (IOI), or require surgical or medical intervention to prevent permanent loss of sight; suspected transmission of an infectious agent by the study drug; and, cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.

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

End point timeframe:

From the date of first administration of faricimab through 28 days after the end of study (up to 2 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned. The adverse events were summarized descriptively.

| End point values                                    | Main Study Cohort A: Faricimab PTI (Prior Faricimab) | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) | Substudy: Faricimab PTI |  |
|-----------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|-------------------------|--|
| Subject group type                                  | Reporting group                                      | Reporting group                                        | Subject analysis set    |  |
| Number of subjects analysed                         | 520                                                  | 505                                                    | 113                     |  |
| Units: participants                                 |                                                      |                                                        |                         |  |
| Any Adverse Event (AE), Any Severity                | 157                                                  | 149                                                    | 17                      |  |
| Serious Adverse Event (SAE)                         | 4                                                    | 11                                                     | 1                       |  |
| Any AE of Special Interest (AESI)                   | 3                                                    | 11                                                     | 1                       |  |
| AESI: Drop in Visual Acuity Score $\geq 30$ Letters | 3                                                    | 8                                                      | 0                       |  |
| AESI: Associated with Severe IOI                    | 0                                                    | 0                                                      | 0                       |  |
| AESI: Intervention Req. to Prev. Perm. Vision Loss  | 0                                                    | 3                                                      | 1                       |  |
| AESI: Suspect. Transm. of Infectious Agent by Drug  | 0                                                    | 0                                                      | 0                       |  |

## Statistical analyses

No statistical analyses for this end point

## Primary: Incidence and Severity of Non-Ocular Adverse Events, with Severity Determined According to Adverse Event Severity Grading Scale

|                 |                                                                                                                                                |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Incidence and Severity of Non-Ocular Adverse Events, with Severity Determined According to Adverse Event Severity Grading Scale <sup>[3]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

This is an analysis of participants with at least one non-ocular (systemic) adverse event (AE). Investigators sought information on AEs at each contact with the participants. All AEs were recorded and the investigator made an assessment of the seriousness, severity (e.g., mild, moderate, or severe intensity), and causality for each AE. AEs of special interest (AESI) included the following: Sight-threatening AEs that cause a drop in visual acuity (VA) score  $\geq 30$  letters lasting more than 1 hour, are associated with severe intraocular inflammation (IOI), or require surgical or medical intervention to prevent permanent loss of sight; suspected transmission of an infectious agent by the study drug; and, cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.

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

End point timeframe:

From the date of first administration of faricimab through 28 days after the end of study (up to 2 years)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No formal statistical hypothesis testing was planned. The adverse events were summarized descriptively.

| End point values                                   | Main Study Cohort A: Faricimab PTI (Prior Faricimab) | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) | Substudy: Faricimab PTI |  |
|----------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|-------------------------|--|
| Subject group type                                 | Reporting group                                      | Reporting group                                        | Subject analysis set    |  |
| Number of subjects analysed                        | 520                                                  | 505                                                    | 113                     |  |
| Units: participants                                |                                                      |                                                        |                         |  |
| Any Adverse Event (AE), Any Severity               | 343                                                  | 337                                                    | 41                      |  |
| AE by Severity: Mild                               | 122                                                  | 120                                                    | 15                      |  |
| AE by Severity: Moderate                           | 138                                                  | 124                                                    | 17                      |  |
| AE by Severity: Severe                             | 83                                                   | 93                                                     | 9                       |  |
| Serious Adverse Event (SAE)                        | 110                                                  | 127                                                    | 13                      |  |
| AE Leading to Withdrawal from Study Treatment      | 3                                                    | 9                                                      | 0                       |  |
| Any AE of Special Interest (AESI)                  | 0                                                    | 0                                                      | 0                       |  |
| AESI: High ALT/AST & High Bilir. or Clin. Jaundice | 0                                                    | 0                                                      | 0                       |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Substudy: Percent Change in Corneal Endothelial Cell Density From Baseline at 1 Year in the Study Eye as Compared With the Fellow Eye

|                 |                                                                                                                                       |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Substudy: Percent Change in Corneal Endothelial Cell Density From Baseline at 1 Year in the Study Eye as Compared With the Fellow Eye |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Specular microscopy was performed for both eyes prior to application of any topical ophthalmic anesthetic, tonometry, or any other study treatment on the same day for the evaluation of corneal endothelial cell density. The 1-year timepoint was defined as the earliest substudy visit closest to Week 52 occurring between Week 48 and Week 64. Data (from both study eye and fellow eye) collected after the fellow eye's use of prohibited therapies—such as faricimab, brolucizumab, bevacizumab, and Port Delivery System implantation—were excluded from the corneal endothelial cell analysis. Modified Intent-to-Treat Population: All enrolled participants who received at least one injection of faricimab in the study eye during this substudy. Only participants who completed the Year 1 visit within the analysis window (Weeks 48 to 64) were included for analysis.

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

End point timeframe:

Baseline and 1 year

| End point values                      | Substudy: Faricimab PTI in the Study Eye | Substudy: Fellow Eye  |  |  |
|---------------------------------------|------------------------------------------|-----------------------|--|--|
| Subject group type                    | Subject analysis set                     | Subject analysis set  |  |  |
| Number of subjects analysed           | 99                                       | 99                    |  |  |
| Units: Percent change in cell density |                                          |                       |  |  |
| number (confidence interval 95%)      | -0.51 (-1.68 to 0.65)                    | -0.71 (-1.53 to 0.10) |  |  |

## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                    |                                                                 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                  | Difference in Percent Change CEC Density at 1 Year              |
| Statistical analysis description:<br>No formal hypothesis testing was planned for this study. The paired t-tests were for reference purposes and thus not considered formal. The test was 2-sided, with the null hypothesis of no difference in percent change from baseline between the study eye and fellow eye in each patient. |                                                                 |
| Comparison groups                                                                                                                                                                                                                                                                                                                  | Substudy: Faricimab PTI in the Study Eye v Substudy: Fellow Eye |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                            | 198                                                             |
| Analysis specification                                                                                                                                                                                                                                                                                                             | Pre-specified                                                   |
| Analysis type                                                                                                                                                                                                                                                                                                                      |                                                                 |
| P-value                                                                                                                                                                                                                                                                                                                            | = 0.7702                                                        |
| Method                                                                                                                                                                                                                                                                                                                             | Paired t-test                                                   |
| Parameter estimate                                                                                                                                                                                                                                                                                                                 | Mean difference (final values)                                  |
| Point estimate                                                                                                                                                                                                                                                                                                                     | 0.2                                                             |
| Confidence interval                                                                                                                                                                                                                                                                                                                |                                                                 |
| level                                                                                                                                                                                                                                                                                                                              | 95 %                                                            |
| sides                                                                                                                                                                                                                                                                                                                              | 2-sided                                                         |
| lower limit                                                                                                                                                                                                                                                                                                                        | -1.14                                                           |
| upper limit                                                                                                                                                                                                                                                                                                                        | 1.54                                                            |

## Secondary: Substudy: Percent Change in Corneal Endothelial Cell Density From Baseline at Week 24 in the Study Eye as Compared With the Fellow Eye

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Substudy: Percent Change in Corneal Endothelial Cell Density From Baseline at Week 24 in the Study Eye as Compared With the Fellow Eye |
| End point description:<br>Specular microscopy was performed for both eyes prior to application of any topical ophthalmic anesthetic, tonometry, or any other study treatment on the same day for the evaluation of corneal endothelial cell density. The Week 24 timepoint was defined as the earliest substudy visit closest to Week 24 occurring between Week 20 and Week 28. Data (from both study eye and fellow eye) collected after the fellow eye's use of prohibited therapies—such as faricimab, brolucizumab, bevacizumab, and Port Delivery System implantation—were excluded from the corneal endothelial cell analysis. Modified Intent-to-Treat Population: All enrolled participants who received at least one injection of faricimab in the study eye during this substudy. Only participants who completed the midpoint visit within the analysis window (Weeks 20 to 28) were included for analysis. |                                                                                                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Secondary                                                                                                                              |
| End point timeframe:<br>Baseline and Week 24                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                        |

| End point values                      | Substudy:<br>Faricimab PTI<br>in the Study<br>Eye | Substudy:<br>Fellow Eye  |  |  |
|---------------------------------------|---------------------------------------------------|--------------------------|--|--|
| Subject group type                    | Subject analysis set                              | Subject analysis set     |  |  |
| Number of subjects analysed           | 103                                               | 103                      |  |  |
| Units: Percent change in cell density |                                                   |                          |  |  |
| number (confidence interval 95%)      | -0.02 (-0.86 to<br>0.81)                          | -0.29 (-0.92 to<br>0.81) |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                                                                    | Difference in Percent Change CEC Density, 24 Weeks              |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                                                                                                             |                                                                 |
| No formal hypothesis testing was planned for this study. The paired t-tests were for reference purposes and thus not considered formal. The test was 2-sided, with the null hypothesis of no difference in percent change from baseline between the study eye and fellow eye in each patient. |                                                                 |
| Comparison groups                                                                                                                                                                                                                                                                             | Substudy: Faricimab PTI in the Study Eye v Substudy: Fellow Eye |
| Number of subjects included in analysis                                                                                                                                                                                                                                                       | 206                                                             |
| Analysis specification                                                                                                                                                                                                                                                                        | Pre-specified                                                   |
| Analysis type                                                                                                                                                                                                                                                                                 |                                                                 |
| P-value                                                                                                                                                                                                                                                                                       | = 0.6305                                                        |
| Method                                                                                                                                                                                                                                                                                        | Paired t-test                                                   |
| Parameter estimate                                                                                                                                                                                                                                                                            | Mean difference (final values)                                  |
| Point estimate                                                                                                                                                                                                                                                                                | 0.27                                                            |
| Confidence interval                                                                                                                                                                                                                                                                           |                                                                 |
| level                                                                                                                                                                                                                                                                                         | 95 %                                                            |
| sides                                                                                                                                                                                                                                                                                         | 2-sided                                                         |
| lower limit                                                                                                                                                                                                                                                                                   | -0.84                                                           |
| upper limit                                                                                                                                                                                                                                                                                   | 1.38                                                            |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the date of first administration of faricimab through 28 days after the end of study (up to 2 years)

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

### Reporting groups

|                       |                                                      |
|-----------------------|------------------------------------------------------|
| Reporting group title | Main Study Cohort A: Faricimab PTI (Prior Faricimab) |
|-----------------------|------------------------------------------------------|

Reporting group description:

This cohort included participants previously randomized to Arm A (faricimab up to every 16 weeks [Q16W]) in the parent studies [GR40306 (NCT03823287) or GR40844 (NCT03823300)]. In this long-term extension study, faricimab 6 mg was administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                       |                                                        |
|-----------------------|--------------------------------------------------------|
| Reporting group title | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) |
|-----------------------|--------------------------------------------------------|

Reporting group description:

This cohort included participants previously randomized to Arm B (aflibercept Q8W) in the parent studies [GR40306 (NCT03823287) or GR40844 (NCT03823300)]. In this long-term extension study, faricimab 6 mg was administered by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Substudy: Faricimab PTI |
|-----------------------|-------------------------|

Reporting group description:

Participants from the main long-term extension study who also consented to participate in this substudy received faricimab 6 mg by intravitreal (IVT) injection into the study eye according to the personalized treatment interval (PTI) dosing regimen for the duration of the study. The fellow eyes of enrolled participants in the substudy were used as a comparator. At the discretion of the principal investigator, fellow eyes were allowed to be treated with standard of care anti-VEGF therapy (if needed) according to region-specific prescribing information. Administration of the following therapies to the fellow eye were prohibited during the substudy: faricimab, brolucizumab, bevacizumab, and Port Delivery System implantation.

| Serious adverse events                                              | Main Study Cohort A: Faricimab PTI (Prior Faricimab) | Main Study Cohort B: Faricimab PTI (Prior Aflibercept) | Substudy: Faricimab PTI |
|---------------------------------------------------------------------|------------------------------------------------------|--------------------------------------------------------|-------------------------|
| Total subjects affected by serious adverse events                   |                                                      |                                                        |                         |
| subjects affected / exposed                                         | 125 / 520 (24.04%)                                   | 156 / 505 (30.89%)                                     | 14 / 113 (12.39%)       |
| number of deaths (all causes)                                       | 13                                                   | 27                                                     | 1                       |
| number of deaths resulting from adverse events                      | 13                                                   | 27                                                     | 1                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                                      |                                                        |                         |
| Ameloblastoma                                                       |                                                      |                                                        |                         |
| subjects affected / exposed                                         | 1 / 520 (0.19%)                                      | 0 / 505 (0.00%)                                        | 0 / 113 (0.00%)         |
| occurrences causally related to treatment / all                     | 0 / 1                                                | 0 / 0                                                  | 0 / 0                   |
| deaths causally related to treatment / all                          | 0 / 0                                                | 0 / 0                                                  | 0 / 0                   |
| Basal cell carcinoma                                                |                                                      |                                                        |                         |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder neoplasm                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain cancer metastatic                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain neoplasm                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Breast cancer                                   |                 |                 |                 |
| subjects affected / exposed                     | 4 / 520 (0.77%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colorectal cancer                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholangiocarcinoma                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colon cancer                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colon neoplasm                                  |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colorectal adenocarcinoma                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervix carcinoma                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Gastric cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Eyelid tumour                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric neoplasm                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| Lung neoplasm                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung carcinoma cell type unspecified stage IV   |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung cancer metastatic                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Lung adenocarcinoma                             |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Invasive ductal breast carcinoma                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mantle cell lymphoma                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatic carcinoma metastatic                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Pancreatic carcinoma                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metastatic neoplasm                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Metastases to lung                              |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meningioma benign                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meningioma                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostatic adenoma                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer recurrent                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small cell carcinoma                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urethral cancer recurrent                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transitional cell carcinoma                     |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tongue neoplasm malignant stage unspecified     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small cell lung cancer                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Peripheral arterial occlusive disease           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Orthostatic hypotension                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intermittent claudication                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic stenosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Deep vein thrombosis                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Giant cell arteritis                            |                 |                 |                 |

|                                                      |                 |                 |                 |
|------------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematoma                                            |                 |                 |                 |
| subjects affected / exposed                          | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension                                         |                 |                 |                 |
| subjects affected / exposed                          | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension                                          |                 |                 |                 |
| subjects affected / exposed                          | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery thrombosis                         |                 |                 |                 |
| subjects affected / exposed                          | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery occlusion                          |                 |                 |                 |
| subjects affected / exposed                          | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral ischaemia                                 |                 |                 |                 |
| subjects affected / exposed                          | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Surgical and medical procedures                      |                 |                 |                 |
| Knee arthroplasty                                    |                 |                 |                 |
| subjects affected / exposed                          | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Asthenia                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chest pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Death                                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 3 / 505 (0.59%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 3           | 0 / 0           |
| General physical health deterioration           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Physical deconditioning                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Acquired hydrocele                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Benign prostatic hyperplasia                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostatic disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 4 / 505 (0.79%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Asthma                                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchial hyperreactivity                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Chronic respiratory failure                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Dyspnoea                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Pleural effusion                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Pulmonary oedema                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 3 / 520 (0.58%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Completed suicide                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Depressive delusion                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Confusional state                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Delirium                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Product issues                                  |                 |                 |                 |
| Device dislocation                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                                |                 |                 |                 |
|----------------------------------------------------------------|-----------------|-----------------|-----------------|
| Device loosening<br>subjects affected / exposed                | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                                 |                 |                 |                 |
| Blood sodium decreased<br>subjects affected / exposed          | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac murmur<br>subjects affected / exposed                  | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Inflammatory marker increased<br>subjects affected / exposed   | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Influenza A virus test positive<br>subjects affected / exposed | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural<br>complications              |                 |                 |                 |
| Failed back surgery syndrome<br>subjects affected / exposed    | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Contusion<br>subjects affected / exposed                       | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to<br>treatment / all             | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |
| Concussion<br>subjects affected / exposed                      | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           | 0 / 0           |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| Compression fracture                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall                                            |                 |                 |                 |
| subjects affected / exposed                     | 4 / 520 (0.77%) | 7 / 505 (1.39%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 7           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hand fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 2 / 505 (0.40%) | 0 / 113 (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           |
| Head injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 3 / 520 (0.58%) | 3 / 505 (0.59%) | 0 / 113 (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           |
| Road traffic accident                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 1           |
| Rib fracture                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Postoperative wound complication                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumothorax traumatic                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Periprosthetic fracture                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pelvic fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meniscus injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Humerus fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury                                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper limb fracture                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Stoma obstruction                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skeletal injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Shoulder fracture                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (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           |
| Toxicity to various agents                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ulna fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (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 / 520 (0.19%) | 4 / 505 (0.79%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arrhythmia                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 3 / 520 (0.58%) | 5 / 505 (0.99%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 6 / 520 (1.15%) | 7 / 505 (1.39%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 7           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 3 / 520 (0.58%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardio-respiratory arrest                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 6 / 505 (1.19%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 4           | 0 / 0           |
| Coronary artery stenosis                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic left ventricular failure                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiovascular disorder                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Sinus node dysfunction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Carotid artery stenosis                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (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           |
| Balance disorder                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aphasia                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebral infarction                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Cerebral haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Headache                                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Generalised tonic-clonic seizure                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 5 / 520 (0.96%) | 5 / 505 (0.99%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 6           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Drop attacks                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dementia Alzheimer's type                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cognitive disorder                              |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Encephalopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Seizure                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular dementia                               |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vertebrobasilar insufficiency                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nerve compression                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myasthenia gravis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolic encephalopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoaesthesia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia vitamin B12 deficiency                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Anaemia                                         |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Dry age-related macular degeneration            |                 |                 |                 |
| subjects affected / exposed                     | 3 / 520 (0.58%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Choroidal neovascularisation                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Choroidal detachment                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cataract                                        |                 |                 |                 |
| subjects affected / exposed                     | 5 / 520 (0.96%) | 7 / 505 (1.39%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5           | 2 / 7           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Age-related macular degeneration                |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dry eye                                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Non-infectious endophthalmitis                  |                 |                 |                 |

|                                                 |                 |                  |                 |
|-------------------------------------------------|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%)  | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Neovascular age-related macular degeneration    |                 |                  |                 |
| subjects affected / exposed                     | 4 / 520 (0.77%) | 14 / 505 (2.77%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 14           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Iridocyclitis                                   |                 |                  |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%)  | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Glaucoma                                        |                 |                  |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%)  | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Retinal aneurysm                                |                 |                  |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%)  | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Subretinal fibrosis                             |                 |                  |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%)  | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Retinal tear                                    |                 |                  |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%)  | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Retinal pigment epithelial tear                 |                 |                  |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%)  | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| Retinal detachment                              |                 |                  |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal degeneration                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Visual acuity reduced                           |                 |                 |                 |
| subjects affected / exposed                     | 3 / 520 (0.58%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Uveitis                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic gastritis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis                                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (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           |
| Colitis ulcerative                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diarrhoea                                       |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulum intestinal                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric ulcer                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenogastric reflux                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastric ulcer haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Intestinal dilatation                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastritis                                       |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Irritable bowel syndrome                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Obstructive pancreatitis                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis acute                             |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Decubitus ulcer                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin ulcer                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 3 / 520 (0.58%) | 4 / 505 (0.79%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder perforation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephritic syndrome                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (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 colic                                     |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Haematoma muscle                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc degeneration                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal disorder                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rhabdomyolysis                                  |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rheumatoid arthritis                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spondylolisthesis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Synovial cyst                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (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                     |                 |                 |                 |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 1 / 505 (0.20%) | 0 / 113 (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           |
| Arthritis bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis bacterial                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis                                      |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 520 (0.38%) | 1 / 505 (0.20%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19                                        |                 |                 |                 |
| subjects affected / exposed                     | 8 / 520 (1.54%) | 5 / 505 (0.99%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 5           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 3 / 505 (0.59%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Postoperative wound infection                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pseudomonal bacteraemia                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis                                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 3 / 505 (0.59%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Pyelonephritis acute                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Febrile infection                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 6 / 520 (1.15%) | 9 / 505 (1.78%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 9           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 0           |
| Clostridium difficile colitis                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dermo-hypodermatitis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endophthalmitis                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 520 (0.38%) | 3 / 505 (0.59%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteomyelitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral uveitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 3 / 520 (0.58%) | 4 / 505 (0.79%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinusitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |

|                                                 |                 |                 |                 |
|-------------------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 520 (0.58%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Bacterial infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 0 / 505 (0.00%) | 1 / 113 (0.88%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Electrolyte imbalance                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 2 / 505 (0.40%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypophosphataemia                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 520 (0.00%) | 1 / 505 (0.20%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Malnutrition                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Starvation                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 520 (0.19%) | 0 / 505 (0.00%) | 0 / 113 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                                                       | Main Study Cohort<br>A: Faricimab PTI<br>(Prior Faricimab) | Main Study Cohort<br>B: Faricimab PTI<br>(Prior Aflibercept) | Substudy: Faricimab<br>PTI |
|-----------------------------------------------------------------------------------------|------------------------------------------------------------|--------------------------------------------------------------|----------------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 158 / 520 (30.38%)                                         | 169 / 505 (33.47%)                                           | 9 / 113 (7.96%)            |
| Eye disorders                                                                           |                                                            |                                                              |                            |
| Cataract                                                                                |                                                            |                                                              |                            |
| subjects affected / exposed                                                             | 56 / 520 (10.77%)                                          | 63 / 505 (12.48%)                                            | 2 / 113 (1.77%)            |
| occurrences (all)                                                                       | 78                                                         | 80                                                           | 2                          |
| Posterior capsule opacification                                                         |                                                            |                                                              |                            |
| subjects affected / exposed                                                             | 14 / 520 (2.69%)                                           | 26 / 505 (5.15%)                                             | 1 / 113 (0.88%)            |
| occurrences (all)                                                                       | 17                                                         | 30                                                           | 1                          |
| Neovascular age-related macular<br>degeneration                                         |                                                            |                                                              |                            |
| subjects affected / exposed                                                             | 60 / 520 (11.54%)                                          | 55 / 505 (10.89%)                                            | 2 / 113 (1.77%)            |
| occurrences (all)                                                                       | 70                                                         | 65                                                           | 3                          |
| Infections and infestations                                                             |                                                            |                                                              |                            |
| COVID-19                                                                                |                                                            |                                                              |                            |
| subjects affected / exposed                                                             | 61 / 520 (11.73%)                                          | 48 / 505 (9.50%)                                             | 5 / 113 (4.42%)            |
| occurrences (all)                                                                       | 65                                                         | 49                                                           | 5                          |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 04 February 2021 | Version 2: -The EUDRACT number, 2020-004523-16, and the study name, AVONELLE-X, have been added to the protocol cover page, protocol acceptance form, and protocol synopsis.; -Section 4.5.6.1 and Appendix 1 have been updated to specify that the optional aqueous humor is to be collected from the study eye.; -A Safety Follow-up visit has been added after the final dose of study treatment to ensure adequate patient safety monitoring.; -Appendix 1 has been updated to remove the optional pharmacokinetic (PK) plasma sample collection at Week 12 as this sample was a duplicate to the mandatory plasma PK sample collected at the same visit.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 15 July 2022     | Version 3: -The option of a dosing interval of Q4W was added to the PTI algorithm.; -Instructions were added that it is not possible for a site to manually modify the PTI algorithm to adjust the faricimab treatment interval.; -The definition for baseline was revised to Day 1 of this study for patients randomized to faricimab in the parent study and as the first day of faricimab treatment for patients randomized to aflibercept in the parent study.; -The risks associated with faricimab were updated to align with Faricimab IB version 11.; -The timeframe for the exclusion of patients who were pregnant or breastfeeding, or intending to become pregnant was extended from within 28 days to within 3 months after the final dose.; -The window for early termination visit was updated to a minimum of 28 days after receiving the final dose of study drug.; -The timing of reporting AEs, SAEs, and AESIs was revised to begin after enrollment in this study, not after initiation of study drug.; -The reporting of AEs associated with a special situation that also qualify as AESI has been revised and should be reported to the Sponsor within 24 hours.; -To align with the responsibility of the PI for the overall safety of the patients, it was clarified that the treatment administrator must be an ophthalmologist, and, ideally, a retina specialist, and it is the PI's responsibility to ensure that the treatment administrator is suitably qualified.; -Therapies that claim to have an effect on macular pathology (e.g., kallidinogenase) were added as a prohibited therapy.; -The types of ocular assessments were clarified, with ultra-wide photography of CFP and FFA imaging permitted only when no other alternative is available.; -The purpose of unscheduled safety visits was revised, specifying that they should only be used for the assessment of AEs and are not intended for standard-of-care procedures.; -CFP was added as an assessment that may be performed during an unscheduled safety assessment visit. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported