



## Clinical trial results:

### A Multicenter, Open-Label Extension Study to Evaluate the Long-Term Safety and Tolerability of Faricimab in Patients with Diabetic Macular Edema

#### Summary

|                          |                                  |
|--------------------------|----------------------------------|
| EudraCT number           | 2020-000402-29                   |
| Trial protocol           | PT CZ DE DK HU GB SK AT PL BG IT |
| Global end of trial date | 11 October 2023                  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 23 October 2024 |
| First version publication date | 23 October 2024 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | GR41987 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04432831 |
| 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                       | 11 October 2023 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 11 October 2023 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 11 October 2023 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the long term ocular and systemic safety and tolerability of faricimab administered intravitreally in patients with DME

Protection of trial subjects:

This study was conducted in full conformance with the ICH E6 guideline for Good Clinical Practice (GCP) 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. An Informed Consent Form (ICF) was required to be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 05 August 2020 |
| 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: 76          |
| Country: Number of subjects enrolled | Australia: 23          |
| Country: Number of subjects enrolled | Austria: 8             |
| Country: Number of subjects enrolled | Bulgaria: 18           |
| Country: Number of subjects enrolled | Brazil: 45             |
| Country: Number of subjects enrolled | Canada: 16             |
| Country: Number of subjects enrolled | Czechia: 56            |
| Country: Number of subjects enrolled | Denmark: 2             |
| Country: Number of subjects enrolled | France: 10             |
| Country: Number of subjects enrolled | Germany: 11            |
| Country: Number of subjects enrolled | Hong Kong: 10          |
| Country: Number of subjects enrolled | Hungary: 61            |
| Country: Number of subjects enrolled | Israel: 33             |
| Country: Number of subjects enrolled | Italy: 21              |
| Country: Number of subjects enrolled | Japan: 48              |
| Country: Number of subjects enrolled | Korea, Republic of: 25 |
| Country: Number of subjects enrolled | Mexico: 10             |
| Country: Number of subjects enrolled | Peru: 12               |
| Country: Number of subjects enrolled | Poland: 166            |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Portugal: 20           |
| Country: Number of subjects enrolled | Russian Federation: 27 |
| Country: Number of subjects enrolled | Singapore: 6           |
| Country: Number of subjects enrolled | Slovakia: 26           |
| Country: Number of subjects enrolled | Spain: 49              |
| Country: Number of subjects enrolled | Switzerland: 1         |
| Country: Number of subjects enrolled | Thailand: 14           |
| Country: Number of subjects enrolled | Türkiye: 15            |
| Country: Number of subjects enrolled | Taiwan: 16             |
| Country: Number of subjects enrolled | United Kingdom: 43     |
| Country: Number of subjects enrolled | United States: 606     |
| Worldwide total number of subjects   | 1474                   |
| EEA total number of subjects         | 448                    |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 750 |
| From 65 to 84 years                       | 714 |
| 85 years and over                         | 10  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 1479 patients were enrolled, but 5 participants in total were excluded from the analysis populations because of Good Clinical Practice (GCP) non-compliance at a single site.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Not applicable                 |
| Blinding used                | Not blinded                    |

### Arms

|                              |                                     |
|------------------------------|-------------------------------------|
| Are arms mutually exclusive? | Yes                                 |
| <b>Arm title</b>             | Faricimab PTI (prior Faricimab Q8W) |

Arm description:

This analysis group includes participants who were previously randomized to Arm A (faricimab 6 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

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

Participants will receive 6 mg faricimab intravitreal injections according to a personalized treatment interval (PTI) dosing regimen.

|                  |                                     |
|------------------|-------------------------------------|
| <b>Arm title</b> | Faricimab PTI (prior Faricimab PTI) |
|------------------|-------------------------------------|

Arm description:

This analysis group includes participants who were previously randomized to Arm B (faricimab 6 mg PTI) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

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

Participants will receive 6 mg faricimab intravitreal injections according to a personalized treatment interval (PTI) dosing regimen.

|                  |                                       |
|------------------|---------------------------------------|
| <b>Arm title</b> | Faricimab PTI (prior Aflibercept Q8W) |
|------------------|---------------------------------------|

Arm description:

This analysis group includes participants who were previously randomized to Arm C (aflibercept 2 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

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

Participants will receive 6 mg faricimab intravitreal injections according to a personalized treatment interval (PTI) dosing regimen.

| <b>Number of subjects in period 1</b>    | Faricimab PTI (prior Faricimab Q8W) | Faricimab PTI (prior Faricimab PTI) | Faricimab PTI (prior Aflibercept Q8W) |
|--|-------------------------------------|-------------------------------------|---------------------------------------|
| Started                                  | 493                                 | 506                                 | 475                                   |
| Received at Least One Dose of Study Drug | 491                                 | 500                                 | 473                                   |
| Completed                                | 405                                 | 407                                 | 392                                   |
| Not completed                            | 88                                  | 99                                  | 83                                    |
| Adverse event, serious fatal             | 23                                  | 23                                  | 17                                    |
| Consent withdrawn by subject             | 24                                  | 28                                  | 21                                    |
| Physician decision                       | 1                                   | 3                                   | 6                                     |
| Adverse event, non-fatal                 | 7                                   | 7                                   | 7                                     |
| Final End of Study Visit Not Completed   | 10                                  | 11                                  | 7                                     |
| Pregnancy                                | -                                   | 1                                   | -                                     |
| Lost to follow-up                        | 15                                  | 15                                  | 12                                    |
| Reason not specified                     | 7                                   | 11                                  | 9                                     |
| Protocol deviation                       | 1                                   | -                                   | 2                                     |
| Lack of efficacy                         | -                                   | -                                   | 2                                     |

## Baseline characteristics

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Faricimab PTI (prior Faricimab Q8W) |
|-----------------------|-------------------------------------|

Reporting group description:

This analysis group includes participants who were previously randomized to Arm A (faricimab 6 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Faricimab PTI (prior Faricimab PTI) |
|-----------------------|-------------------------------------|

Reporting group description:

This analysis group includes participants who were previously randomized to Arm B (faricimab 6 mg PTI) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Faricimab PTI (prior Aflibercept Q8W) |
|-----------------------|---------------------------------------|

Reporting group description:

This analysis group includes participants who were previously randomized to Arm C (aflibercept 2 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

| Reporting group values                             | Faricimab PTI (prior Faricimab Q8W) | Faricimab PTI (prior Faricimab PTI) | Faricimab PTI (prior Aflibercept Q8W) |
|--|-------------------------------------|-------------------------------------|---------------------------------------|
| Number of subjects                                 | 493                                 | 506                                 | 475                                   |
| 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)                               | 264                                 | 243                                 | 243                                   |
| From 65-84 years                                   | 223                                 | 261                                 | 230                                   |
| 85 years and over                                  | 6                                   | 2                                   | 2                                     |
| Age Continuous                                     |                                     |                                     |                                       |
| Units: Years                                       |                                     |                                     |                                       |
| arithmetic mean                                    | 63.4                                | 64.0                                | 63.5                                  |
| standard deviation                                 | ± 9.9                               | ± 9.8                               | ± 9.4                                 |
| Sex: Female, Male                                  |                                     |                                     |                                       |
| Units: Participants                                |                                     |                                     |                                       |
| Female   | 191                                 | 184                                 | 205                                   |
| Male   | 302                                 | 322                                 | 270                                   |
| Race (NIH/OMB)                                     |                                     |                                     |                                       |
| Units: Subjects                                    |                                     |                                     |                                       |
| American Indian or Alaska Native                   | 5                                   | 4                                   | 4                                     |
| Asian  | 54                                  | 52                                  | 45                                    |
| Native Hawaiian or Other Pacific Islander          | 1                                   | 0                                   | 1                                     |
| Black or African American                          | 27                                  | 32                                  | 25                                    |

|                         |     |     |     |
|-------------------------|-----|-----|-----|
| White                   | 392 | 406 | 389 |
| More than one race      | 1   | 0   | 0   |
| Unknown or Not Reported | 13  | 12  | 11  |
| Ethnicity (NIH/OMB)     |     |     |     |
| Units: Subjects         |     |     |     |
| Hispanic or Latino      | 68  | 87  | 79  |
| Not Hispanic or Latino  | 415 | 408 | 386 |
| Unknown or Not Reported | 10  | 11  | 10  |

|   |       |  |  |
|---|-------|--|--|
| <b>Reporting group values</b>                         | Total |  |  |
| Number of subjects                                    | 1474  |  |  |
| Age categorical                                       |       |  |  |
| Units: Subjects                                       |       |  |  |
| In utero  | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                                  | 0     |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0     |  |  |
| Children (2-11 years)                                 | 0     |  |  |
| Adolescents (12-17 years)                             | 0     |  |  |
| Adults (18-64 years)                                  | 750   |  |  |
| From 65-84 years                                      | 714   |  |  |
| 85 years and over                                     | 10    |  |  |
| Age Continuous  |       |  |  |
| Units: Years  |       |  |  |
| arithmetic mean                                       |       |  |  |
| standard deviation                                    | -     |  |  |
| Sex: Female, Male                                     |       |  |  |
| Units: Participants                                   |       |  |  |
| Female  | 580   |  |  |
| Male  | 894   |  |  |
| Race (NIH/OMB)  |       |  |  |
| Units: Subjects                                       |       |  |  |
| American Indian or Alaska Native                      | 13    |  |  |
| Asian   | 151   |  |  |
| Native Hawaiian or Other Pacific<br>Islander          | 2     |  |  |
| Black or African American                             | 84    |  |  |
| White   | 1187  |  |  |
| More than one race                                    | 1     |  |  |
| Unknown or Not Reported                               | 36    |  |  |
| Ethnicity (NIH/OMB)                                   |       |  |  |
| Units: Subjects                                       |       |  |  |
| Hispanic or Latino                                    | 234   |  |  |
| Not Hispanic or Latino                                | 1209  |  |  |
| Unknown or Not Reported                               | 31    |  |  |

## End points

### End points reporting groups

|   |                                       |
|---|---------------------------------------|
| Reporting group title   | Faricimab PTI (prior Faricimab Q8W)   |
| Reporting group description:<br>This analysis group includes participants who were previously randomized to Arm A (faricimab 6 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.   |                                       |
| Reporting group title   | Faricimab PTI (prior Faricimab PTI)   |
| Reporting group description:<br>This analysis group includes participants who were previously randomized to Arm B (faricimab 6 mg PTI) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.   |                                       |
| Reporting group title   | Faricimab PTI (prior Aflibercept Q8W) |
| Reporting group description:<br>This analysis group includes participants who were previously randomized to Arm C (aflibercept 2 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen. |                                       |

### 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:<br>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:<br>From the day of the first dose of faricimab until the end of the study (up to 108 weeks)  |   |

#### 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: There was no formal hypothesis testing planned for this study. This safety end point was assessed through descriptive summaries of the number of adverse events.

| End point values                     | Faricimab PTI (prior Faricimab Q8W) | Faricimab PTI (prior Faricimab PTI) | Faricimab PTI (prior Aflibercept Q8W) |  |
|--------------------------------------|-------------------------------------|-------------------------------------|---------------------------------------|--|
| Subject group type                   | Reporting group                     | Reporting group                     | Reporting group                       |  |
| Number of subjects analysed          | 491                                 | 500                                 | 473                                   |  |
| Units: Participants                  |                                     |                                     |                                       |  |
| Any Adverse Event (AE), Any Severity | 219                                 | 188                                 | 197                                   |  |
| AE by Severity: Mild                 | 119                                 | 109                                 | 109                                   |  |
| AE by Severity: Moderate             | 74                                  | 66                                  | 74                                    |  |



|   |    |    |    |  |
|---|----|----|----|--|
| AE by Severity: Severe                              | 20 | 10 | 12 |  |
| AE by Severity: Missing                             | 6  | 3  | 2  |  |
| Serious Adverse Event (SAE)                         | 31 | 15 | 26 |  |
| AE Leading to Withdrawal from Study Treatment       | 3  | 0  | 6  |  |
| Treatment-related AE                                | 10 | 10 | 11 |  |
| Treatment-related SAE                               | 0  | 1  | 1  |  |
| Any AE of Special Interest (AESI)                   | 30 | 14 | 24 |  |
| AESI: Drop in Visual Acuity Score $\geq 30$ Letters | 23 | 10 | 20 |  |
| AESI: Associated with Severe IOI                    | 1  | 1  | 1  |  |
| AESI: Intervention Req. to Prev. Perm. Vision Loss  | 6  | 3  | 3  |  |
| 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 fellow eye (i.e., non-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 day of the first dose of faricimab until the end of the study (up to 108 weeks)

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: There was no formal hypothesis testing planned for this study. This safety end point was assessed through descriptive summaries of the number of adverse events.

| End point values                                    | Faricimab PTI (prior Faricimab Q8W) | Faricimab PTI (prior Faricimab PTI) | Faricimab PTI (prior Aflibercept Q8W) |  |
|---|-------------------------------------|-------------------------------------|---------------------------------------|--|
| Subject group type                                  | Reporting group                     | Reporting group                     | Reporting group                       |  |
| Number of subjects analysed                         | 491                                 | 500                                 | 473                                   |  |
| Units: Participants                                 |                                     |                                     |                                       |  |
| Any Adverse Event (AE)                              | 186                                 | 185                                 | 179                                   |  |
| Serious Adverse Event (SAE)                         | 16                                  | 17                                  | 15                                    |  |
| Any AE of Special Interest (AESI)                   | 13                                  | 16                                  | 14                                    |  |
| AESI: Drop in Visual Acuity Score $\geq 30$ Letters | 6                                   | 9                                   | 10                                    |  |
| AESI: Associated with Severe IOI                    | 0                                   | 1                                   | 1                                     |  |

|  |   |   |   |  |
|--|---|---|---|--|
| AESI: Intervention Req. to Prev. Perm. Vision Loss | 7 | 6 | 4 |  |
| 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 day of the first dose of faricimab until the end of the study (up to 108 weeks)

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: There was no formal hypothesis testing planned for this study. This safety end point was assessed through descriptive summaries of the number of adverse events.

| End point values                                    | Faricimab PTI (prior Faricimab Q8W) | Faricimab PTI (prior Faricimab PTI) | Faricimab PTI (prior Aflibercept Q8W) |  |
|---|-------------------------------------|-------------------------------------|---------------------------------------|--|
| Subject group type                                  | Reporting group                     | Reporting group                     | Reporting group                       |  |
| Number of subjects analysed                         | 491                                 | 500                                 | 473                                   |  |
| Units: Participants                                 |                                     |                                     |                                       |  |
| Any Adverse Event (AE), Any Severity                | 317                                 | 295                                 | 297                                   |  |
| AE by Severity: Mild                                | 91                                  | 94                                  | 97                                    |  |
| AE by Severity: Moderate                            | 124                                 | 124                                 | 115                                   |  |
| AE by Severity: Severe                              | 102                                 | 77                                  | 85                                    |  |
| Serious Adverse Event (SAE)                         | 122                                 | 100                                 | 112                                   |  |
| AE Leading to Withdrawal from Study Treatment       | 2                                   | 7                                   | 4                                     |  |
| Any AE of Special Interest (AESI)                   | 0                                   | 0                                   | 1                                     |  |
| AESI: Drop in Visual Acuity Score $\geq 30$ Letters | 0                                   | 0                                   | 1                                     |  |
| AESI: High ALT/AST & High Bilir. or Clin. Jaundice  | 0                                   | 0                                   | 0                                     |  |

## Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the day of the first dose of faricimab until the end of the study (up to 108 weeks)

Adverse event reporting additional description:

Total number of deaths and adverse events (AEs) are reported for the Safety-Evaluable Population, which included all participant who enrolled and received at least one dose of faricimab during the study. For ocular AEs, the number of participants and events reported per term are specified to have occurred in the study eye or the fellow eye.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.1 |
|--------------------|------|

### Reporting groups

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Faricimab PTI (prior Faricimab Q8W) |
|-----------------------|-------------------------------------|

Reporting group description:

This analysis group includes participants who were previously randomized to Arm A (faricimab 6 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

|                       |                                     |
|-----------------------|-------------------------------------|
| Reporting group title | Faricimab PTI (prior Faricimab PTI) |
|-----------------------|-------------------------------------|

Reporting group description:

This analysis group includes participants who were previously randomized to Arm B (faricimab 6 mg PTI) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

|                       |                                       |
|-----------------------|---------------------------------------|
| Reporting group title | Faricimab PTI (prior Aflibercept Q8W) |
|-----------------------|---------------------------------------|

Reporting group description:

This analysis group includes participants who were previously randomized to Arm C (aflibercept 2 mg Q8W) in one of the parent studies, GR40349 (NCT03622580) and GR40398 (NCT03622593), and then enrolled in this extension study to receive faricimab 6 mg by IVT injection according to the personalized treatment interval (PTI) dosing regimen.

| Serious adverse events  | Faricimab PTI (prior Faricimab Q8W) | Faricimab PTI (prior Faricimab PTI) | Faricimab PTI (prior Aflibercept Q8W) |
|---|-------------------------------------|-------------------------------------|---------------------------------------|
| Total subjects affected by serious adverse events                   |                                     |                                     |                                       |
| subjects affected / exposed   | 158 / 491 (32.18%)                  | 124 / 500 (24.80%)                  | 134 / 473 (28.33%)                    |
| number of deaths (all causes)                                       | 22                                  | 20                                  | 17                                    |
| number of deaths resulting from adverse events                      |                                     |                                     |                                       |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                     |                                     |                                       |
| Chronic lymphocytic leukaemia                                       |                                     |                                     |                                       |
| subjects affected / exposed   | 0 / 491 (0.00%)                     | 0 / 500 (0.00%)                     | 1 / 473 (0.21%)                       |
| occurrences causally related to treatment / all                     | 0 / 0                               | 0 / 0                               | 0 / 1                                 |
| deaths causally related to treatment / all                          | 0 / 0                               | 0 / 0                               | 0 / 0                                 |
| Clear cell renal cell carcinoma                                     |                                     |                                     |                                       |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Adenocarcinoma of colon                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Benign anorectal neoplasm                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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 cancer metastatic                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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                     | 0 / 491 (0.00%) | 4 / 500 (0.80%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Breast neoplasm                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Bladder transitional cell carcinoma             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endometrial cancer stage III                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Gastric cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Gastric cancer stage IV                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic cancer                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Hepatocellular carcinoma                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Leukaemia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Neoplasm malignant                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Neuroendocrine carcinoma of the skin            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Oesophageal cancer metastatic                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Ovarian fibroma                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Pancreatic carcinoma                            |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 2 / 500 (0.40%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal cancer stage IV                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Spinal cord neoplasm                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Uterine leiomyoma                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal adenocarcinoma                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Angiopathy                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Hypertensive urgency                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral arterial occlusive disease           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery occlusion                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Aortic stenosis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Arteriosclerosis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Circulatory collapse                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Deep vein thrombosis                            |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension                                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 1 / 500 (0.20%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive crisis                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive emergency                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery stenosis                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral artery thrombosis                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Shock   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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 vascular disorder                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral ischaemia                            |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 491 (0.20%) | 3 / 500 (0.60%) | 0 / 473 (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           |
| General disorders and administration site conditions |                 |                 |                 |
| Chest discomfort                                     |                 |                 |                 |
| subjects affected / exposed                          | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Organ failure  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Death  |                 |                 |                 |
| subjects affected / exposed                          | 3 / 491 (0.61%) | 5 / 500 (1.00%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all      | 0 / 3           | 0 / 5           | 0 / 2           |
| deaths causally related to treatment / all           | 0 / 3           | 0 / 5           | 0 / 2           |
| Hernia   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Impaired healing                                     |                 |                 |                 |
| subjects affected / exposed                          | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Malaise  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Multiple organ dysfunction syndrome                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Oedema peripheral                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 2 / 500 (0.40%) | 0 / 473 (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           |
| Chest pain                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Systemic inflammatory response syndrome         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Immune system disorders                         |                 |                 |                 |
| Food allergy                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Drug hypersensitivity                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Contrast media allergy                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Allergy to arthropod sting                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Reproductive system and breast disorders        |                 |                 |                 |
| Orchitis noninfective                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Pelvic cyst                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Uterine polyp                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Hypoxia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Chronic respiratory failure                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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 obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 2 / 500 (0.40%) | 0 / 473 (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           |
| Asthma  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute respiratory failure                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 1 / 500 (0.20%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |

|                                      |   |                 |                 |                 |
|--------------------------------------|---|-----------------|-----------------|-----------------|
| Atelectasis                          | subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
|                                      | occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
|                                      | deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pleural effusion                     | subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Pneumothorax                         | subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
|                                      | 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                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Pulmonary fibrosis                   | subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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                     | 2 / 491 (0.41%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Respiratory failure                  | subjects affected / exposed                     | 2 / 491 (0.41%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Psychiatric disorders                |   |                 |                 |                 |
| Substance-induced psychotic disorder |   |                 |                 |                 |
|                                      | subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Mental status changes                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Product issues                                  |                 |                 |                 |
| Device leakage                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Ammonia increased                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Glycosylated haemoglobin abnormal               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Heart rate increased                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| SARS-CoV-2 test positive                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Precancerous cells present                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| Liver function test abnormal<br>subjects affected / exposed | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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           |
| Intraocular pressure increased                              | Additional description: SAEs occurred in the fellow eye |                 |                 |
| subjects affected / exposed                                 | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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           |
| Red blood cell count decreased                              |   |                 |                 |
| subjects affected / exposed                                 | 0 / 491 (0.00%)   | 1 / 500 (0.20%) | 0 / 473 (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           |
| Injury, poisoning and procedural<br>complications           |   |                 |                 |
| Contusion   |   |                 |                 |
| subjects affected / exposed                                 | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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           |
| Corneal abrasion  | Additional description: SAEs occurred in the fellow eye |                 |                 |
| subjects affected / exposed                                 | 0 / 491 (0.00%)   | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to<br>treatment / all          | 0 / 0   | 0 / 1           | 0 / 1           |
| deaths causally related to<br>treatment / all               | 0 / 0   | 0 / 0           | 0 / 0           |
| Brain contusion   |   |                 |                 |
| subjects affected / exposed                                 | 0 / 491 (0.00%)   | 1 / 500 (0.20%) | 0 / 473 (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           |
| Cataract traumatic  | Additional description: SAEs occurred the study eye     |                 |                 |
| subjects affected / exposed                                 | 0 / 491 (0.00%)   | 1 / 500 (0.20%) | 0 / 473 (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           |
| Comminuted fracture   |   |                 |                 |
| subjects affected / exposed                                 | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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           |

| Eye injury                                      | Additional description: SAEs occurred the study eye |                 |                 |
|---|---|-----------------|-----------------|
|   |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)                                     | 0 / 500 (0.00%) | 0 / 473 (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           |
| Fall  |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)                                     | 1 / 500 (0.20%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Femoral neck fracture                           |   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)                                     | 2 / 500 (0.40%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Femur fracture                                  |   |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%)                                     | 1 / 500 (0.20%) | 0 / 473 (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           |
| Foot fracture                                   |   |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%)                                     | 0 / 500 (0.00%) | 0 / 473 (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           |
| Foreign body                                    |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)                                     | 0 / 500 (0.00%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Fracture displacement                           |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)                                     | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Hand fracture                                   |   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)                                     | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Head injury                                     |   |                 |                 |



|   |   |                 |                 |
|---|---|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%)   | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Patella fracture                                |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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           |
| Ocular procedural complication                  | Additional description: SAEs occurred in the fellow eye |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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 vertebral fracture                       |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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                     | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Radius fracture                                 |   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)   | 1 / 500 (0.20%) | 0 / 473 (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           |
| Peritoneal dialysis complication                |   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)   | 1 / 500 (0.20%) | 0 / 473 (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           |
| Post procedural constipation                    |   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)   | 1 / 500 (0.20%) | 0 / 473 (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           |
| Post procedural inflammation                    | Additional description: SAEs occurred in the fellow eye |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Pelvic fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Spinal compression fracture                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Skull fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Shoulder fracture                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Road traffic accident                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Tendon rupture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Wound necrosis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular procedure complication                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Toxicity to various agents                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Tibia fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Atrioventricular block complete                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 4 / 473 (0.85%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arteriosclerosis coronary artery                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 4 / 500 (0.80%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 2 / 500 (0.40%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute left ventricular failure                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 2 / 500 (0.40%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorder                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Cardiac discomfort                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 2 / 500 (0.40%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 2           | 0 / 0           |
| Bradycardia                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bradyarrhythmia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block second degree            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 7 / 491 (1.43%) | 3 / 500 (0.60%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 4           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 1           | 0 / 0           |
| Cardiac tamponade                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac valve disease                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 2           |
| Cardiogenic shock                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Cardiac failure                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 3 / 500 (0.60%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure acute                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 6 / 491 (1.22%) | 5 / 500 (1.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 5           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ventricular hypokinesia                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Tachycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pericardial effusion                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 9 / 491 (1.83%) | 3 / 500 (0.60%) | 8 / 473 (1.69%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 3           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 1           | 0 / 3           |
| Ischaemic cardiomyopathy                        |                 |                 |                 |

|   |                 |                 |                  |
|---|-----------------|-----------------|------------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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            |
| Coronary artery stenosis                        |                 |                 |                  |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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            |
| Coronary artery occlusion                       |                 |                 |                  |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 0 / 473 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Nervous system disorders                        |                 |                 |                  |
| Carotid artery stenosis                         |                 |                 |                  |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%)  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Amyotrophic lateral sclerosis                   |                 |                 |                  |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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            |
| Encephalomalacia                                |                 |                 |                  |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Cerebrovascular accident                        |                 |                 |                  |
| subjects affected / exposed                     | 4 / 491 (0.81%) | 3 / 500 (0.60%) | 10 / 473 (2.11%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           | 1 / 10           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 3            |
| Cerebral infarction                             |                 |                 |                  |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 0 / 500 (0.00%) | 1 / 473 (0.21%)  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0            |
| Haemorrhage intracranial                        |                 |                 |                  |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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           |
| Lethargy  |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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           |
| Hepatic encephalopathy                          |   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)   | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Hypoaesthesia                                   |   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)   | 1 / 500 (0.20%) | 0 / 473 (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           |
| Hypoglycaemic unconsciousness                   |   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)   | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0   | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)   | 1 / 500 (0.20%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke                             |   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1   | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           | 0 / 0           |
| Optic neuritis                                  | Additional description: SAEs occurred in the fellow eye |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)   | 0 / 500 (0.00%) | 0 / 473 (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           |
| Migraine  |   |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Leukoencephalopathy                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Paraparesis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Toxic encephalopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 2 / 500 (0.40%) | 0 / 473 (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           |
| Status epilepticus                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Seizure   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vertebral artery stenosis                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vocal cord paralysis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 2 / 500 (0.40%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Iron deficiency anaemia                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Leukocytosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombocytopenia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrogenic anaemia                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Normocytic anaemia                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Neutropenia                                     |                 |                 |                 |

|   |  |                  |                  |
|---|--|------------------|------------------|
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%)  | 0 / 473 (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            |
| Eye disorders                                   |  |                  |                  |
| Cataract  | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 11[491]11, 8[500]8, 15[473]15) and the fellow eye (subjects affected [exposed] occurrences = 1[491]1, 6[500]6, 0[473]0) |                  |                  |
| subjects affected / exposed                     | 12 / 491 (2.44%)   | 14 / 500 (2.80%) | 15 / 473 (3.17%) |
| occurrences causally related to treatment / all | 0 / 12   | 0 / 14           | 0 / 15           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            | 0 / 0            |
| Diabetic retinal oedema                         | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 7[491]8, 0[500]0, 2[473]2) and the fellow eye (subjects affected [exposed] occurrences = 1[491]1, 1[500]1, 2[473]2)     |                  |                  |
| subjects affected / exposed                     | 8 / 491 (1.63%)  | 1 / 500 (0.20%)  | 4 / 473 (0.85%)  |
| occurrences causally related to treatment / all | 0 / 9  | 0 / 1            | 0 / 4            |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            | 0 / 0            |
| Cataract nuclear                                | Additional description: SAEs occurred in the study eye   |                  |                  |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%)  | 0 / 473 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            | 0 / 0            |
| Cataract cortical                               | Additional description: SAEs occurred in the fellow eye  |                  |                  |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%)  | 0 / 473 (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            |
| Angle closure glaucoma                          | Additional description: SAEs occurred in the fellow eye  |                  |                  |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 1 / 500 (0.20%)  | 0 / 473 (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            |
| Neovascular age-related macular degeneration    | Additional description: SAEs occurred in the fellow eye  |                  |                  |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%)  | 0 / 473 (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            |
| Posterior capsule opacification                 | Additional description: SAEs occurred in the study eye   |                  |                  |
| subjects affected / exposed                     | 2 / 491 (0.41%)  | 0 / 500 (0.00%)  | 0 / 473 (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            |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| Iridocyclitis                                   | Additional description: SAEs occurred in the study eye   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Iridocele                                       | Additional description: SAEs occurred in the study eye   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Glaucoma  | Additional description: SAEs occurred in the study eye   |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 1 / 500 (0.20%) | 0 / 473 (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           |
| Rhegmatogenous retinal detachment               | Additional description: SAEs occurred in the study eye   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Retinal tear                                    | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 0[491]0, 1[500]1, 0[473]0) and the fellow eye (subjects affected [exposed] occurrences = 0[491]0, 1[500]1, 0[473]0) |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 1 / 500 (0.20%) | 0 / 473 (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 neovascularisation                      | Additional description: SAEs occurred in the fellow eye  |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 1 / 500 (0.20%) | 0 / 473 (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           |
| Tractional retinal detachment                   | Additional description: SAEs occurred in the fellow eye  |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%)  | 0 / 500 (0.00%) | 0 / 473 (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           |
| Diabetic retinopathy                            | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 0[491]0, 0[500]0, 1[473]1) and the fellow eye (subjects affected [exposed] occurrences = 2[491]2, 3[500]3, 2[473]2) |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%)  | 3 / 500 (0.60%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 2  | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| Epiretinal membrane                             | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 0[491]0, 0[500]0, 1[473]1) and the fellow eye (subjects affected [exposed] occurrences = 0[491]0, 0[500]0, 2[473]2) |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 0 / 500 (0.00%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Retinal artery occlusion                        | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 0[491]0, 1[500]1, 2[473]2) and the fellow eye (subjects affected [exposed] occurrences = 1[491]1, 0[500]0, 1[473]1) |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 1 / 500 (0.20%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1  | 1 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Retinal detachment                              | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 2[491]2, 0[500]0, 0[473]0) and the fellow eye (subjects affected [exposed] occurrences = 1[491]1, 0[500]0, 1[473]1) |                 |                 |
| subjects affected / exposed                     | 3 / 491 (0.61%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 3  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Retinal vein occlusion                          | Additional description: SAEs occurred in the study eye   |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%)  | 1 / 500 (0.20%) | 0 / 473 (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           |
| Vitreous haemorrhage                            | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 1[491]1, 1[500]1, 2[473]2) and the fellow eye (subjects affected [exposed] occurrences = 4[491]4, 3[500]3, 6[473]6) |                 |                 |
| subjects affected / exposed                     | 5 / 491 (1.02%)  | 4 / 500 (0.80%) | 8 / 473 (1.69%) |
| occurrences causally related to treatment / all | 0 / 5  | 0 / 4           | 0 / 8           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Uveitis   | Additional description: SAEs occurred in the study eye   |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1  | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |  |                 |                 |
| Faecaloma                                       |  |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Gastrointestinal haemorrhage                    |  |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Haematochezia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Haemorrhoidal haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal perforation                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophagitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colitis   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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 ulcerative                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Constipation                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Oral mucosal hypertrophy                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Umbilical hernia                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Volvulus  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Portal vein thrombosis                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Hepatic cirrhosis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Gallbladder rupture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Biliary tract disorder                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Cellulite                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic foot                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 3 / 500 (0.60%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin ulcer                                      |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 3 / 491 (0.61%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Diabetic nephropathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic kidney disease                          |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 3 / 500 (0.60%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 8 / 491 (1.63%) | 5 / 500 (1.00%) | 5 / 473 (1.06%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 5           | 0 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| End stage renal disease                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 2 / 500 (0.40%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ureterolithiasis                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subcapsular renal haematoma                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal impairment                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal haemorrhage                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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 failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 3 / 491 (0.61%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephropathy                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 3 / 500 (0.60%) | 0 / 473 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Back pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Spinal stenosis                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pain in extremity                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Neuropathic arthropathy                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Neck pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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 chest pain                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Infections and infestations                     |                 |                 |                 |
| Abdominal abscess                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Abscess limb                                    |                 |                 |                 |

|   |                  |                 |                 |
|---|------------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Abdominal infection                             |                  |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%) | 0 / 473 (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           |
| Bacteraemia                                     |                  |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| COVID-19  |                  |                 |                 |
| subjects affected / exposed                     | 10 / 491 (2.04%) | 9 / 500 (1.80%) | 5 / 473 (1.06%) |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 9           | 0 / 5           |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 3           | 0 / 0           |
| Arthritis infective                             |                  |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 1 / 500 (0.20%) | 0 / 473 (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           |
| Arthritis bacterial                             |                  |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%)  | 0 / 500 (0.00%) | 0 / 473 (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           |
| Bronchitis                                      |                  |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Atypical pneumonia                              |                  |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           | 0 / 0           |
| Diabetic gangrene                               |                  |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis intestinal haemorrhagic          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Diabetic foot infection                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Device related sepsis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Clostridium difficile colitis                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Cholecystitis infective                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 3 / 491 (0.61%) | 4 / 500 (0.80%) | 6 / 473 (1.27%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19 pneumonia                              |                 |                 |                 |

|   |  |                 |                 |
|---|--|-----------------|-----------------|
| subjects affected / exposed                     | 4 / 491 (0.81%)  | 2 / 500 (0.40%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 4  | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 1  | 0 / 0           | 0 / 0           |
| Erysipelas                                      |  |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Endocarditis bacterial                          |  |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Endocarditis                                    |  |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%)  | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0  | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Endophthalmitis                                 | Additional description: SAEs occurred in both the study eye (subjects affected [exposed] occurrences = 2[491]2, 0[500]0, 1[473]1) and the fellow eye (subjects affected [exposed] occurrences = 2[491]2, 0[500]0, 1[473]1) |                 |                 |
| subjects affected / exposed                     | 4 / 491 (0.81%)  | 0 / 500 (0.00%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 1 / 4  | 0 / 0           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Infected skin ulcer                             |  |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%)  | 0 / 500 (0.00%) | 0 / 473 (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           |
| Gangrene  |  |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 2 / 500 (0.40%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Gastroenteritis norovirus                       |  |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%)  | 0 / 500 (0.00%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1  | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0           | 0 / 0           |
| Infected dermal cyst                            |  |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 2 / 500 (0.40%) | 0 / 473 (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           |
| Febrile infection                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Neutropenic sepsis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Localised infection                             |                 |                 |                 |
| subjects affected / exposed                     | 7 / 491 (1.43%) | 0 / 500 (0.00%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Labyrinthitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteomyelitis                                   |                 |                 |                 |
| subjects affected / exposed                     | 7 / 491 (1.43%) | 4 / 500 (0.80%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peritonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Paronychia                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteomyelitis chronic                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteomyelitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Systemic bacterial infection                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic endocarditis                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 4 / 491 (0.81%) | 2 / 500 (0.40%) | 4 / 473 (0.85%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 1           |
| Staphylococcal infection                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Pneumonia aspiration                            |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 2 / 500 (0.40%) | 0 / 473 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Pneumonia bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Pyelonephritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 5 / 491 (1.02%) | 8 / 500 (1.60%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 9           | 0 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 2 / 491 (0.41%) | 0 / 500 (0.00%) | 3 / 473 (0.63%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wound infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Dehydration                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Malnutrition                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypoglycaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 1 / 500 (0.20%) | 2 / 473 (0.42%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Hypervolaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperkalaemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 2 / 500 (0.40%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperglycaemic hyperosmolar nonketotic syndrome |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyperglycaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 0 / 500 (0.00%) | 1 / 473 (0.21%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetic ketoacidosis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 491 (0.20%) | 0 / 500 (0.00%) | 0 / 473 (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           |
| Diabetes mellitus inadequate control            |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |
| Diabetes mellitus                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 491 (0.00%) | 1 / 500 (0.20%) | 0 / 473 (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           |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events                            | Faricimab PTI (prior Faricimab Q8W)   | Faricimab PTI (prior Faricimab PTI) | Faricimab PTI (prior Aflibercept Q8W) |
|---|---|-------------------------------------|---------------------------------------|
| Total subjects affected by non-serious adverse events |   |                                     |                                       |
| subjects affected / exposed                           | 233 / 491 (47.45%)  | 213 / 500 (42.60%)                  | 219 / 473 (46.30%)                    |
| Investigations  |   |                                     |                                       |
| Intraocular pressure increased                        | Additional description: AEs occurred in the study eye   |                                     |                                       |
| subjects affected / exposed                           | 16 / 491 (3.26%)  | 12 / 500 (2.40%)                    | 12 / 473 (2.54%)                      |
| occurrences (all)                                     | 20  | 15                                  | 13                                    |
| Vascular disorders                                    |   |                                     |                                       |
| Hypertension  |   |                                     |                                       |
| subjects affected / exposed                           | 18 / 491 (3.67%)  | 20 / 500 (4.00%)                    | 23 / 473 (4.86%)                      |
| occurrences (all)                                     | 18  | 20                                  | 24                                    |
| Eye disorders   |   |                                     |                                       |
| Cataract  | Additional description: AEs occurred in both the study eye (subjects affected [exposed] occurrences = 65[491]65, 60[500]60, 63[473]63) and the fellow eye (subjects affected [exposed] occurrences = 56[491]56, 41[500]41, 51[473]52) |                                     |                                       |
| subjects affected / exposed                           | 90 / 491 (18.33%)   | 72 / 500 (14.40%)                   | 84 / 473 (17.76%)                     |
| occurrences (all)                                     | 115   | 91                                  | 110                                   |
| Posterior capsule opacification                       | Additional description: AEs occurred in both the study eye (subjects affected [exposed] occurrences = 16[491]17, 17[500]17, 14[473]14) and the fellow eye (subjects affected [exposed] occurrences = 13[491]14, 20[500]20, 13[473]13) |                                     |                                       |
| subjects affected / exposed                           | 19 / 491 (3.87%)  | 29 / 500 (5.80%)                    | 20 / 473 (4.23%)                      |
| occurrences (all)                                     | 27  | 34                                  | 27                                    |
| Diabetic retinal oedema                               | Additional description: AEs occurred in the fellow eye  |                                     |                                       |
| subjects affected / exposed                           | 22 / 491 (4.48%)  | 27 / 500 (5.40%)                    | 24 / 473 (5.07%)                      |
| occurrences (all)                                     | 22  | 31                                  | 27                                    |
| Conjunctival haemorrhage                              | Additional description: AEs occurred in the study eye   |                                     |                                       |
| subjects affected / exposed                           | 16 / 491 (3.26%)  | 9 / 500 (1.80%)                     | 5 / 473 (1.06%)                       |
| occurrences (all)                                     | 17  | 9                                   | 5                                     |

|   |  |                  |                  |
|---|--|------------------|------------------|
| Diabetic retinopathy<br>subjects affected / exposed<br>occurrences (all)                    | Additional description: AEs occurred in the fellow eye |                  |                  |
|   | 17 / 491 (3.46%)                                       | 8 / 500 (1.60%)  | 12 / 473 (2.54%) |
|   | 17   | 8                | 12               |
| Vitreous detachment<br>subjects affected / exposed<br>occurrences (all)                     | Additional description: AEs occurred in the study eye  |                  |                  |
|   | 16 / 491 (3.26%)                                       | 12 / 500 (2.40%) | 6 / 473 (1.27%)  |
|   | 16   | 12               | 6                |
| Vitreous floaters<br>subjects affected / exposed<br>occurrences (all)                       | Additional description: AEs occurred in the study eye  |                  |                  |
|   | 16 / 491 (3.26%)                                       | 7 / 500 (1.40%)  | 8 / 473 (1.69%)  |
|   | 18   | 7                | 8                |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all) |  |                  |                  |
|   | 63 / 491 (12.83%)                                      | 49 / 500 (9.80%) | 46 / 473 (9.73%) |
|   | 70   | 50               | 49               |
|   |  |                  |                  |
|   |  |                  |                  |
|   |  |                  |                  |
|   |  |                  |                  |
|   |  |                  |                  |
|   |  |                  |                  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                         | 18 / 491 (3.67%)                                       | 12 / 500 (2.40%) | 23 / 473 (4.86%) |
|   | 21   | 12               | 27               |
|   |  |                  |                  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                 | 16 / 491 (3.26%)                                       | 15 / 500 (3.00%) | 16 / 473 (3.38%) |
|   | 19   | 17               | 18               |
|   |  |                  |                  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 13 May 2020      | Protocol Version 2: An exclusion criterion was added relating to a history of reaction or hypersensitivity to biologic agents including any component of the faricimab injection or study treatment procedures.  |
| 13 December 2021 | Protocol Version 3: -A Final End-of-Study (FEOS) visit, to be completed 28-35 days after the last PTI dosing visit, was included for all patients. Therefore, the study was extended to a maximum of 108 weeks for patients who received their final dose of faricimab at Week 104; -The list of prohibited therapies was amended to clarify that continuous usage of topical ophthalmic corticosteroids for 100 days or more is considered prohibited therapy, and to add the use of kallidinogenase and other medications claiming to have an effect on macular pathology to the list of prohibited therapies. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported