



## Clinical trial results:

**Multicenter, randomized, placebo-controlled, double-blind, parallel group, dose-finding Phase 2 study to evaluate efficacy and safety of BAY 2433334 in patients following an acute non-cardioembolic ischemic stroke**

### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2019-003431-33                               |
| Trial protocol           | CZ GB ES PT FI DE NL AT FR HU DK BE BG PL IT |
| Global end of trial date | 18 February 2022                             |

### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 03 March 2023 |
| First version publication date | 03 March 2023 |

### Trial information

#### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | BAY2433334/19766 |
|-----------------------|------------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04304508 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Bayer AG   |
| Sponsor organisation address | Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368                 |
| Public contact               | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com |
| Scientific contact           | Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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                       | 20 March 2022    |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 18 February 2022 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To assess the dose-response of 3 different doses of asundexian compared to placebo in reducing the composite of symptomatic ischemic strokes and covert brain infarcts detected by Magnetic resonance imaging (MRI) as well as other cerebro- and cardiovascular endpoints in participants with an acute noncardioembolic ischemic stroke and who are treated with antiplatelet therapy.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy:

Anti-platelet therapy

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 15 June 2020 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Bulgaria: 177           |
| Country: Number of subjects enrolled | Czechia: 68             |
| Country: Number of subjects enrolled | Hungary: 29             |
| Country: Number of subjects enrolled | Poland: 47              |
| Country: Number of subjects enrolled | Russian Federation: 123 |
| Country: Number of subjects enrolled | Slovakia: 80            |
| Country: Number of subjects enrolled | United States: 23       |
| Country: Number of subjects enrolled | Australia: 116          |
| Country: Number of subjects enrolled | Austria: 40             |
| Country: Number of subjects enrolled | Belgium: 51             |
| Country: Number of subjects enrolled | Switzerland: 64         |
| Country: Number of subjects enrolled | Germany: 73             |
| Country: Number of subjects enrolled | Denmark: 79             |
| Country: Number of subjects enrolled | Spain: 216              |
| Country: Number of subjects enrolled | Finland: 36             |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | France: 84         |
| Country: Number of subjects enrolled | United Kingdom: 55 |
| Country: Number of subjects enrolled | Italy: 87          |
| Country: Number of subjects enrolled | Netherlands: 18    |
| Country: Number of subjects enrolled | Portugal: 79       |
| Country: Number of subjects enrolled | Sweden: 9          |
| Country: Number of subjects enrolled | China: 81          |
| Country: Number of subjects enrolled | Japan: 173         |
| Worldwide total number of subjects   | 1808               |
| EEA total number of subjects         | 1173               |

Notes:

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### **Subjects enrolled per age group**

|   |      |
|---|------|
| In utero                                  | 0    |
| Preterm newborn - gestational age < 37 wk | 0    |
| Newborns (0-27 days)                      | 0    |
| Infants and toddlers (28 days-23 months)  | 0    |
| Children (2-11 years)                     | 0    |
| Adolescents (12-17 years)                 | 0    |
| Adults (18-64 years)                      | 709  |
| From 65 to 84 years                       | 1039 |
| 85 years and over                         | 60   |

## Subject disposition

### Recruitment

Recruitment details:

Study was conducted at 197 centers in 23 countries or regions, between 15-Jun-2020 (first subject first visit) and 18-Feb-2022 (last subject last visit)

### Pre-assignment

Screening details:

1880 subjects were screened. 72 subjects were screening failures. 1808 subjects were randomized in a 1:1:1:1 ratio to 4 treatment groups: 455, 450, and 447 subjects to asundexian 10 mg, 20 mg and 50 mg groups, 456 subjects to placebo group. 22 subjects (10, 4, 4 and 4 in the asundexian 10 mg, 20 mg and 50 mg, and placebo groups) never administered.

### Period 1

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

### Arms

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

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Asundexian 10 mg |
|------------------|------------------|

Arm description:

Subjects received Asundexian (BAY2433334) 10 mg for 26 weeks at least and up to 52 weeks

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Asundexian         |
| Investigational medicinal product code | BAY2433334         |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects received Asundexian (BAY2433334) 10 mg (5 mg tablets) orally once daily in the morning

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Asundexian 20 mg |
|------------------|------------------|

Arm description:

Subjects received Asundexian (BAY2433334) 20 mg for 26 weeks at least and up to 52 weeks

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Asundexian         |
| Investigational medicinal product code | BAY2433334         |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects received Asundexian (BAY2433334) 20 mg (5 mg and 15 mg tablets) orally once daily in the morning

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Asundexian 50 mg |
|------------------|------------------|

Arm description:

Subjects received Asundexian (BAY2433334) 50 mg for 26 weeks at least and up to 52 weeks

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Asundexian         |
| Investigational medicinal product code | BAY2433334         |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects received Asundexian (BAY2433334) 50 mg (25 mg tablets) orally once daily in the morning

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Subjects received Asundexian (BAY2433334) placebo for 26 weeks at least and up to 52 weeks

|  |                    |
|--|--------------------|
| Arm type                               | Placebo            |
| Investigational medicinal product name | Placebo            |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Subjects received placebo orally once daily in the morning.

| <b>Number of subjects in period 1</b>         | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg |
|---|------------------|------------------|------------------|
| Started                                       | 455              | 450              | 447              |
| Treated                                       | 445              | 446              | 443              |
| Completed                                     | 335              | 329              | 313              |
| Not completed                                 | 120              | 121              | 134              |
| Physician decision                            | 3                | 4                | 9                |
| Physician Decision: COVID-19 Pandemic Related | 1                | -                | -                |
| Consent withdrawn by subject                  | 7                | 5                | 11               |
| Subject Decision                              | 29               | 39               | 37               |
| Logistical Difficulties                       | 2                | 2                | 3                |
| Adverse event, non-fatal                      | 49               | 50               | 51               |
| Subject Decision: COVID-19 Pandemic Related   | -                | 1                | -                |
| Other   | 7                | 6                | 5                |
| Non-compliance With Study Drug                | 3                | 1                | 2                |
| Death   | 6                | 1                | 8                |
| Missing Information                           | 1                | 2                | 1                |
| Study drug never administered                 | 10               | 4                | 4                |
| Lost to follow-up                             | 1                | 5                | 2                |
| Switching To Other Therapy                    | 1                | 1                | 1                |

| <b>Number of subjects in period 1</b> | Placebo |
|---------------------------------------|---------|
| Started                               | 456     |

|  |     |
|--|-----|
| Treated  | 452 |
| Completed  | 314 |
| Not completed                                    | 142 |
| Physician decision                               | 7   |
| Physician Decision: COVID-19<br>Pandemic Related | -   |
| Consent withdrawn by subject                     | 6   |
| Subject Decision                                 | 48  |
| Logistical Difficulties                          | 2   |
| Adverse event, non-fatal                         | 56  |
| Subject Decision: COVID-19<br>Pandemic Related   | 2   |
| Other  | 4   |
| Non-compliance With Study Drug                   | -   |
| Death  | 5   |
| Missing Information                              | 3   |
| Study drug never administered                    | 4   |
| Lost to follow-up                                | 3   |
| Switching To Other Therapy                       | 2   |

## Baseline characteristics

### Reporting groups

|  |                  |
|--|------------------|
| Reporting group title  | Asundexian 10 mg |
| Reporting group description:   |                  |
| Subjects received Asundexian (BAY2433334) 10 mg for 26 weeks at least and up to 52 weeks   |                  |
| Reporting group title  | Asundexian 20 mg |
| Reporting group description:   |                  |
| Subjects received Asundexian (BAY2433334) 20 mg for 26 weeks at least and up to 52 weeks   |                  |
| Reporting group title  | Asundexian 50 mg |
| Reporting group description:   |                  |
| Subjects received Asundexian (BAY2433334) 50 mg for 26 weeks at least and up to 52 weeks   |                  |
| Reporting group title  | Placebo          |
| Reporting group description:   |                  |
| Subjects received Asundexian (BAY2433334) placebo for 26 weeks at least and up to 52 weeks |                  |

| Reporting group values                                | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg |
|---|------------------|------------------|------------------|
| Number of subjects                                    | 455              | 450              | 447              |
| Age Categorical<br>Units: Subjects                    |                  |                  |                  |
| In utero  | 0                | 0                | 0                |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                | 0                | 0                |
| Newborns (0-27 days)                                  | 0                | 0                | 0                |
| Infants and toddlers (28 days-23<br>months)           | 0                | 0                | 0                |
| Children (2-11 years)                                 | 0                | 0                | 0                |
| Adolescents (12-17 years)                             | 0                | 0                | 0                |
| Adults (18-64 years)                                  | 186              | 154              | 174              |
| From 65-84 years                                      | 255              | 279              | 258              |
| 85 years and over                                     | 14               | 17               | 15               |
| Gender Categorical<br>Units: Subjects                 |                  |                  |                  |
| Female  | 161              | 150              | 154              |
| Male  | 294              | 300              | 293              |
| Race<br>Units: Subjects                               |                  |                  |                  |
| Asian   | 67               | 67               | 68               |
| Black or African American                             | 4                | 3                | 8                |
| Native Hawaiian or Other Pacific<br>Islander          | 0                | 1                | 1                |
| Not Reported  | 3                | 2                | 3                |
| White   | 381              | 377              | 367              |

| Reporting group values             | Placebo | Total |  |
|------------------------------------|---------|-------|--|
| Number of subjects                 | 456     | 1808  |  |
| Age Categorical<br>Units: Subjects |         |       |  |
| In utero                           | 0       | 0     |  |

|  |     |      |  |
|--|-----|------|--|
| Preterm newborn infants (gestational age < 37 wks) | 0   | 0    |  |
| Newborns (0-27 days)                               | 0   | 0    |  |
| Infants and toddlers (28 days-23 months)           | 0   | 0    |  |
| Children (2-11 years)                              | 0   | 0    |  |
| Adolescents (12-17 years)                          | 0   | 0    |  |
| Adults (18-64 years)                               | 195 | 709  |  |
| From 65-84 years                                   | 247 | 1039 |  |
| 85 years and over                                  | 14  | 60   |  |
| <b>Gender Categorical</b>                          |     |      |  |
| Units: Subjects                                    |     |      |  |
| Female   | 150 | 615  |  |
| Male   | 306 | 1193 |  |
| <b>Race</b>  |     |      |  |
| Units: Subjects                                    |     |      |  |
| Asian  | 66  | 268  |  |
| Black or African American                          | 3   | 18   |  |
| Native Hawaiian or Other Pacific Islander          | 1   | 3    |  |
| Not Reported                                       | 6   | 14   |  |
| White  | 380 | 1505 |  |

### Subject analysis sets

|  |                           |
|--|---------------------------|
| Subject analysis set title   | Full analysis set (FAS)   |
| Subject analysis set type  | Full analysis             |
| Subject analysis set description:  |                           |
| A subject was included in the FAS if he/she was randomized to a treatment group.   |                           |
| Subject analysis set title   | Safety analysis set (SAF) |
| Subject analysis set type  | Safety analysis           |
| Subject analysis set description:  |                           |
| A subject was included in the SAF if he/she was randomized to study intervention and had taken at least one dose of the study intervention.  |                           |
| Subject analysis set title   | Total Asundexian          |
| Subject analysis set type  | Sub-group analysis        |
| Subject analysis set description:  |                           |
| A subject was included in the Total Asundexian if he/she was randomized to Asundexian 10 mg group or Asundexian 20 mg group or Asundexian 50 mg group and had taken at least one dose of Asundexian. |                           |

| Reporting group values                             | Full analysis set (FAS) | Safety analysis set (SAF) | Total Asundexian |
|--|-------------------------|---------------------------|------------------|
| Number of subjects                                 | 1808                    | 1786                      | 1334             |
| <b>Age Categorical</b>                             |                         |                           |                  |
| Units: Subjects                                    |                         |                           |                  |
| In utero   | 0                       | 0                         |                  |
| Preterm newborn infants (gestational age < 37 wks) | 0                       | 0                         |                  |
| Newborns (0-27 days)                               | 0                       | 0                         |                  |
| Infants and toddlers (28 days-23 months)           | 0                       | 0                         |                  |
| Children (2-11 years)                              | 0                       | 0                         |                  |
| Adolescents (12-17 years)                          | 0                       | 0                         |                  |
| Adults (18-64 years)                               | 709                     | 703                       |                  |

|                   |      |      |  |
|-------------------|------|------|--|
| From 65-84 years  | 1039 | 1024 |  |
| 85 years and over | 60   | 59   |  |

|   |      |      |  |
|---|------|------|--|
| Gender Categorical<br>Units: Subjects     |      |      |  |
| Female                                    | 615  | 608  |  |
| Male                                      | 1193 | 1178 |  |
| Race<br>Units: Subjects                   |      |      |  |
| Asian                                     | 268  | 263  |  |
| Black or African American                 | 18   | 18   |  |
| Native Hawaiian or Other Pacific Islander | 3    | 3    |  |
| Not Reported                              | 14   | 13   |  |
| White                                     | 1505 | 1489 |  |

## End points

### End points reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | Asundexian 10 mg          |
| Reporting group description:   |                           |
| Subjects received Asundexian (BAY2433334) 10 mg for 26 weeks at least and up to 52 weeks   |                           |
| Reporting group title  | Asundexian 20 mg          |
| Reporting group description:   |                           |
| Subjects received Asundexian (BAY2433334) 20 mg for 26 weeks at least and up to 52 weeks   |                           |
| Reporting group title  | Asundexian 50 mg          |
| Reporting group description:   |                           |
| Subjects received Asundexian (BAY2433334) 50 mg for 26 weeks at least and up to 52 weeks   |                           |
| Reporting group title  | Placebo                   |
| Reporting group description:   |                           |
| Subjects received Asundexian (BAY2433334) placebo for 26 weeks at least and up to 52 weeks   |                           |
| Subject analysis set title   | Full analysis set (FAS)   |
| Subject analysis set type  | Full analysis             |
| Subject analysis set description:  |                           |
| A subject was included in the FAS if he/she was randomized to a treatment group.   |                           |
| Subject analysis set title   | Safety analysis set (SAF) |
| Subject analysis set type  | Safety analysis           |
| Subject analysis set description:  |                           |
| A subject was included in the SAF if he/she was randomized to study intervention and had taken at least one dose of the study intervention.  |                           |
| Subject analysis set title   | Total Asundexian          |
| Subject analysis set type  | Sub-group analysis        |
| Subject analysis set description:  |                           |
| A subject was included in the Total Asundexian if he/she was randomized to Asundexian 10 mg group or Asundexian 20 mg group or Asundexian 50 mg group and had taken at least one dose of Asundexian. |                           |

### **Primary: Efficacy-Number of subjects with composite of symptomatic ischemic stroke and covert brain infarcts detected by magnetic resonance imaging (MRI)**

|  |  |
|--|--|
| End point title  | Efficacy-Number of subjects with composite of symptomatic ischemic stroke and covert brain infarcts detected by magnetic resonance imaging (MRI) |
| End point description:   |  |
| Ischemic stroke was defined as either of : 1) Rapid onset (or present on awakening) of a new focal neurological deficit with clinical (>24 hours symptoms/signs) or imaging evidence of infarction that was not attributable to a non-ischemic cause; 2) Acute worsening of an existing focal neurological deficit that was judged to be attributable to a new infarction or extension of the previous infarction in the same vascular territory, based on persisting symptoms/signs or imaging evidence of infarction and no evidence of a non-ischemic etiology. If imaging was inconclusive, persistent symptoms/signs must be significant (worsening of NIHSS score of 4 or more) and sustained (duration of $\geq 24$ hours or until death). Covert brain infarcts were defined as incident infarcts detected by serial MRI in the absence of an adjudicated stroke consistent with the location of the infarct. MRI criteria for brain infarction were available in the MRI procedures manual. |  |
| End point type   | Primary  |
| End point timeframe:   |  |
| From baseline up to 26 weeks   |  |

| <b>End point values</b>     | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 455              | 450              | 447              | 456             |
| Units: Subjects             | 86               | 99               | 90               | 87              |

## Statistical analyses

| <b>Statistical analysis title</b>                             | Ratio of the incidence proportions |
|---|------------------------------------|
| Statistical analysis description:                             |                                    |
| Comparison of the Asundexian 10 mg group versus Placebo group |                                    |
| Comparison groups   | Asundexian 10 mg v Placebo         |
| Number of subjects included in analysis                       | 911                                |
| Analysis specification  | Pre-specified                      |
| Analysis type   | other                              |
| Parameter estimate  | Crude incidence ratio              |
| Point estimate  | 1.044                              |
| Confidence interval   |                                    |
| level   | 90 %                               |
| sides   | 2-sided                            |
| lower limit   | 0.8105                             |
| upper limit   | 1.3478                             |

| <b>Statistical analysis title</b>   | Dose-response test   |
|---|--|
| Statistical analysis description:   |  |
| Dose-response test by using multiple comparison procedures (MCP) Mod method |  |
| Comparison groups   | Asundexian 10 mg v Asundexian 20 mg v Asundexian 50 mg v Placebo |
| Number of subjects included in analysis                                     | 1808   |
| Analysis specification  | Pre-specified  |
| Analysis type   | other  |
| P-value   | = 0.7976   |
| Method  | MCP Mod  |

| <b>Statistical analysis title</b>                             | Ratio of the incidence proportions |
|---|------------------------------------|
| Statistical analysis description:                             |                                    |
| Comparison of the Asundexian 50 mg group versus Placebo group |                                    |
| Comparison groups   | Placebo v Asundexian 50 mg         |
| Number of subjects included in analysis                       | 903                                |
| Analysis specification  | Pre-specified                      |
| Analysis type   | other                              |
| Parameter estimate  | Crude incidence ratio              |
| Point estimate  | 1.0485                             |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.8082  |
| upper limit         | 1.3619  |

|   |                                    |
|---|------------------------------------|
| <b>Statistical analysis title</b>                             | Ratio of the incidence proportions |
| Statistical analysis description:                             |                                    |
| Comparison of the Asundexian 20 mg group versus Placebo group |                                    |
| Comparison groups   | Placebo v Asundexian 20 mg         |
| Number of subjects included in analysis                       | 906                                |
| Analysis specification  | Pre-specified                      |
| Analysis type   | other                              |
| Parameter estimate  | Crude incidence ratio              |
| Point estimate  | 1.1963                             |
| Confidence interval   |                                    |
| level   | 90 %                               |
| sides   | 2-sided                            |
| lower limit   | 0.9281                             |
| upper limit   | 1.5428                             |

**Primary: Safety-Number of subjects with composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding**

|                 |  |
|-----------------|--|
| End point title | Safety-Number of subjects with composite of International Society on Thrombosis and Hemostasis (ISTH) major bleeding and clinically relevant non-major (CRNM) bleeding |
|-----------------|--|

End point description:

ISTH Major Bleeding criteria: 1. Fatal bleeding, and/or 2. Symptomatic bleeding in a critical area or organ (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular, or intramuscular with compartment syndrome), and/or 3. Clinically overt bleeding associated with a recent decrease in the hemoglobin level of  $\geq 2$  g/dL (20 g/L; 1.24 mmol/L) compared to the most recent hemoglobin value available before the event, and/or 4. Clinically overt bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood. ISTH Clinically Relevant Non-Major Bleeding is considered any sign or symptom of hemorrhage that does not fit the criteria for the ISTH definition of major bleeding, but does meet at least one of the following criteria 1. requiring medical intervention by a healthcare professional. 2. leading to hospitalization or increased level of care. 3. prompting a face to face (i.e. not just a telephone or electronic communication) evaluation.

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

End point timeframe:

From baseline up to 52 weeks

| <b>End point values</b>     | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 445              | 446              | 443              | 452             |
| Units: Subjects             | 19               | 14               | 19               | 11              |

| <b>End point values</b>     | Total Asundexian     |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 1334                 |  |  |  |
| Units: Subjects             | 52                   |  |  |  |

## Statistical analyses

| <b>Statistical analysis title</b>                             | Cause specific Hazard ratio (csHR) |
|---|------------------------------------|
| Statistical analysis description:                             |                                    |
| Comparison of the Asundexian 10 mg group versus Placebo group |                                    |
| Comparison groups   | Asundexian 10 mg v Placebo         |
| Number of subjects included in analysis                       | 897                                |
| Analysis specification  | Pre-specified                      |
| Analysis type   | other <sup>[1]</sup>               |
| P-value   | = 0.1507                           |
| Method  | Logrank                            |
| Parameter estimate  | Cox proportional hazard            |
| Point estimate  | 1.724                              |
| Confidence interval   |                                    |
| level   | 90 %                               |
| sides   | 2-sided                            |
| lower limit   | 0.924                              |
| upper limit   | 3.215                              |

Notes:

[1] - Cause specific HRs were only calculated if at least 3 events occurred in 1 of the compared groups and at least 1 event in each of the compared treatment groups.

| <b>Statistical analysis title</b>                             | Cause-specific Hazard Ratio (csHR) |
|---|------------------------------------|
| Statistical analysis description:                             |                                    |
| Comparison of the Asundexian 50 mg group versus Placebo group |                                    |
| Comparison groups   | Asundexian 50 mg v Placebo         |
| Number of subjects included in analysis                       | 895                                |
| Analysis specification  | Pre-specified                      |
| Analysis type   | other <sup>[2]</sup>               |
| P-value   | = 0.1401                           |
| Method  | Logrank                            |
| Parameter estimate  | Cox proportional hazard            |
| Point estimate  | 1.749                              |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.938   |
| upper limit         | 3.262   |

Notes:

[2] - Cause specific HRs were only calculated if at least 3 events occurred in 1 of the compared groups and at least 1 event in each of the compared treatment groups.

|                                   |                                    |
|-----------------------------------|------------------------------------|
| <b>Statistical analysis title</b> | Cause specific Hazard ratio (csHR) |
|-----------------------------------|------------------------------------|

Statistical analysis description:

Comparison of the Total Asundexian group versus Placebo group

|   |                            |
|---|----------------------------|
| Comparison groups                       | Placebo v Total Asundexian |
| Number of subjects included in analysis | 1786                       |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other <sup>[3]</sup>       |
| P-value                                 | = 0.1653                   |
| Method                                  | Logrank                    |
| Parameter estimate                      | Cox proportional hazard    |
| Point estimate                          | 1.585                      |
| Confidence interval                     |                            |
| level                                   | 90 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.918                      |
| upper limit                             | 2.736                      |

Notes:

[3] - Cause specific HRs were only calculated if at least 3 events occurred in 1 of the compared groups and at least 1 event in each of the compared treatment groups.

|                                   |                                    |
|-----------------------------------|------------------------------------|
| <b>Statistical analysis title</b> | Cause-specific hazard ratio (csHR) |
|-----------------------------------|------------------------------------|

Statistical analysis description:

Comparison of the Asundexian 20 mg group versus Placebo group

|   |                            |
|---|----------------------------|
| Comparison groups                       | Asundexian 20 mg v Placebo |
| Number of subjects included in analysis | 898                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | other <sup>[4]</sup>       |
| P-value                                 | = 0.5339                   |
| Method                                  | Logrank                    |
| Parameter estimate                      | Cox proportional hazard    |
| Point estimate                          | 1.285                      |
| Confidence interval                     |                            |
| level                                   | 90 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.662                      |
| upper limit                             | 2.494                      |

Notes:

[4] - Cause specific HRs were only calculated if at least 3 events occurred in 1 of the compared groups and at least 1 event in each of the compared treatment groups.

**Secondary: Efficacy-Number of subjects with composite of symptomatic ischemic stroke and covert brain infarcts detected by MRI, cardiovascular (CV) death, Myocardial infarction (MI) and systemic embolism.**

|                 |   |
|-----------------|---|
| End point title | Efficacy-Number of subjects with composite of symptomatic |
|-----------------|---|

ischemic stroke and covert brain infarcts detected by MRI, cardiovascular (CV) death, Myocardial infarction (MI) and systemic embolism.

End point description:

CV death included death due to stroke, MI, heart failure or cardiogenic shock, sudden death or any other death due to other cardiovascular causes. Death due to non-traumatic hemorrhage was included. Acute MI was used when there was evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. According to MI Universal Definition from 2018 the diagnosis of MI required the combination of: 1) Presence of acute myocardial injury, and 2) Evidence of acute myocardial ischemia derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging, or in case of post-mortem pathological findings irrespective of biomarker values. Systemic embolism was defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms (this did not include thromboembolism of the pulmonary vasculature or venous thrombosis).

End point type Secondary

End point timeframe:

From baseline up to 26 weeks

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 455              | 450              | 447              | 456             |
| Units: Subjects             | 80               | 87               | 81               | 79              |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Efficacy-Number of subjects with symptomatic ischemic stroke

End point title Efficacy-Number of subjects with symptomatic ischemic stroke

End point description:

Definition of symptomatic ischemic stroke can be referred to first Primary endpoint.

End point type Secondary

End point timeframe:

From baseline up to 52 weeks

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 455              | 450              | 447              | 456             |
| Units: Subjects             | 26               | 26               | 22               | 28              |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Efficacy-Number of subjects with symptomatic ischemic stroke, CV death, MI**

---

|                 |  |
|-----------------|--|
| End point title | Efficacy-Number of subjects with symptomatic ischemic stroke, CV death, MI |
|-----------------|--|

End point description:

Definition of symptomatic ischemic stroke can be referred to first Primary endpoint. Definition of CV death and MI can be referred to first Second endpoint.

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

End point timeframe:

From baseline up to 52 weeks

---

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 455              | 450              | 447              | 456             |
| Units: Subjects             | 33               | 30               | 33               | 35              |

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**Statistical analyses**

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No statistical analyses for this end point

---

**Secondary: Efficacy-Number of subjects with covert brain infarcts detected by MRI**

---

|                 |  |
|-----------------|--|
| End point title | Efficacy-Number of subjects with covert brain infarcts detected by MRI |
|-----------------|--|

End point description:

Definition of covert brain infarcts can be referred to first Primary endpoint.

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

End point timeframe:

From baseline up to 26 weeks

---

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 455              | 450              | 447              | 456             |
| Units: Subjects             | 62               | 68               | 63               | 60              |

---

**Statistical analyses**

---

No statistical analyses for this end point

## Secondary: Efficacy-Number of subjects with symptomatic ischemic and hemorrhagic stroke

|                 |  |
|-----------------|--|
| End point title | Efficacy-Number of subjects with symptomatic ischemic and hemorrhagic stroke |
|-----------------|--|

End point description:

Definition of symptomatic ischemic can be referred to fourth secondary endpoint. Hemorrhagic stroke was defined as an acute, atraumatic extravasation of blood into the brain parenchyma, intraventricular or subarachnoid space with associated neurological symptoms. This did not include microbleeds or hemorrhagic transformation of an ischemic stroke.

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

End point timeframe:

From baseline up to 52 weeks

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 455              | 450              | 447              | 456             |
| Units: Subjects             | 26               | 26               | 25               | 30              |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Efficacy-Number of subjects with Disabling stroke (mRS≥4)

|                 |   |
|-----------------|---|
| End point title | Efficacy-Number of subjects with Disabling stroke (mRS≥4) |
|-----------------|---|

End point description:

Modified ranking score (mRS): 0-No symptoms at all; 1-No significant disability despite symptoms; despite symptoms, able to carry out all usual duties and activities; 2-Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance; 3-Moderate disability; requiring some help, but able to walk without assistance; 4-Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance; 5-Severe disability; bedridden, incontinent and requiring constant nursing care and attention; 6-Death.

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

End point timeframe:

From baseline up to 52 weeks

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 455              | 450              | 447              | 456             |
| Units: Subjects             | 5                | 5                | 1                | 3               |

## Statistical analyses

No statistical analyses for this end point

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**Secondary: Efficacy-Number of subjects with All-cause mortality**

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End point title Efficacy-Number of subjects with All-cause mortality

End point description:

End point type Secondary

End point timeframe:

From baseline up to 52 weeks

---

| <b>End point values</b>     | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 455              | 450              | 447              | 456             |
| Units: Subjects             | 10               | 6                | 17               | 10              |

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Safety-Number of subjects with all bleeding**

---

End point title Safety-Number of subjects with all bleeding

End point description:

All bleeding events occurred from first intake of study intervention until 2 days after the last intake of study intervention.

End point type Secondary

End point timeframe:

From baseline up to 52 weeks

---

| <b>End point values</b>     | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 445              | 446              | 443              | 452             |
| Units: Subjects             | 37               | 48               | 48               | 44              |

| <b>End point values</b>     | Total Asundexian     |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 1334                 |  |  |  |
| Units: Subjects             | 133                  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Safety-Number of subjects with ISTH major bleeding

End point title Safety-Number of subjects with ISTH major bleeding

End point description:

Definition of ISTH major bleeding can be referred to second Primary endpoint.

End point type Secondary

End point timeframe:

From baseline up to 52 weeks

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 445              | 446              | 443              | 452             |
| Units: Subjects             | 4                | 3                | 7                | 4               |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Safety-Number of subjects with ISTH CRNM bleeding

End point title Safety-Number of subjects with ISTH CRNM bleeding

End point description:

Definition of ISTH CRNM bleeding can be referred to second Primary endpoint.

End point type Secondary

End point timeframe:

From baseline up to 52 weeks

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 445              | 446              | 443              | 452             |
| Units: Subjects             | 15               | 12               | 12               | 7               |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Safety-Number of subjects with ISTH minor bleeding

|                 |  |
|-----------------|--|
| End point title | Safety-Number of subjects with ISTH minor bleeding |
|-----------------|--|

End point description:

All other overt bleeding episodes not meeting the above criteria for ISTH major or CRNM bleeding were classified as minor bleeding (e.g. bleeding from a minor wound that does not prompt a face-to-face evaluation for a physical examination or laboratory testing).

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

End point timeframe:

From baseline up to 52 weeks

| End point values            | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 445              | 446              | 443              | 452             |
| Units: Subjects             | 21               | 39               | 34               | 34              |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Safety-Number of subjects with Intracerebral hemorrhage (non-traumatic)

|                 |   |
|-----------------|---|
| End point title | Safety-Number of subjects with Intracerebral hemorrhage (non-traumatic) |
|-----------------|---|

End point description:

Non-traumatic intracerebral hemorrhage was defined as a hemorrhagic stroke on the "recurrent stroke" CRF page that is in addition classified as a bleeding with bleeding site intracranial (-subarachnoid, -intraparenchymal [excluding microbleeds], or -intraventricular) and spontaneous causality of bleeding, excluding all symptomatic and hemorrhagic transformation (defined by the PT "hemorrhagic transformation").

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

End point timeframe:

From baseline up to 52 weeks

| <b>End point values</b>     | Asundexian 10 mg | Asundexian 20 mg | Asundexian 50 mg | Placebo         |
|-----------------------------|------------------|------------------|------------------|-----------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group |
| Number of subjects analysed | 445              | 446              | 443              | 452             |
| Units: Subjects             | 0                | 0                | 3                | 1               |

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

After the first administration of study intervention for up to 52 weeks (but not starting after more than 2 days after the last administration).

Adverse event reporting additional description:

Reporting for the deaths (all causes) considers all deaths that occurred at any time during the study before the last contact, for up to 54 weeks.

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Asundexian 10 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received Asundexian (BAY2433334) 10 mg for 26 weeks at least and up to 52 weeks

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received Asundexian (BAY2433334) placebo for 26 weeks at least and up to 52 weeks

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Asundexian 50 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received Asundexian (BAY2433334) 50 mg for 26 weeks at least and up to 52 weeks

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Asundexian 20 mg |
|-----------------------|------------------|

Reporting group description:

Subjects received Asundexian (BAY2433334) 20 mg for 26 weeks at least and up to 52 weeks

| <b>Serious adverse events</b>                                       | Asundexian 10 mg  | Placebo           | Asundexian 50 mg  |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events                   |                   |                   |                   |
| subjects affected / exposed   | 90 / 445 (20.22%) | 98 / 452 (21.68%) | 93 / 443 (20.99%) |
| number of deaths (all causes)                                       | 10                | 10                | 17                |
| number of deaths resulting from adverse events                      | 5                 | 7                 | 12                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |                   |
| Gastric cancer  |                   |                   |                   |
| subjects affected / exposed   | 0 / 445 (0.00%)   | 0 / 452 (0.00%)   | 0 / 443 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 0             | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 0             | 0 / 0             |
| Endometrial adenocarcinoma  |                   |                   |                   |
| subjects affected / exposed   | 1 / 445 (0.22%)   | 0 / 452 (0.00%)   | 0 / 443 (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             |
| Glioblastoma multiforme   |                   |                   |                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Metastases to central nervous system            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung cancer metastatic                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Rectal cancer                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophageal adenocarcinoma                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung adenocarcinoma                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Brain neoplasm                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Thymoma malignant</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Colorectal cancer</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Lung neoplasm</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Metastasis</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Invasive ductal breast carcinoma</b>         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Vascular disorders</b>                       |                 |                 |                 |
| <b>Hypertensive crisis</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hypertension</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Aortic thrombosis</b>                        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Peripheral ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Extremity necrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Deep vein thrombosis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Venous thrombosis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Thrombophlebitis                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Atheroembolism                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Surgical and medical procedures                 |                 |                 |                 |
| Atrial septal defect repair                     |                 |                 |                 |
| subjects affected / exposed                     | 5 / 445 (1.12%) | 1 / 452 (0.22%) | 3 / 443 (0.68%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac pacemaker insertion                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 445 (0.45%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Carotid endarterectomy</b>                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Hip arthroplasty</b>                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Endarterectomy</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Coronary artery bypass</b>                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Cholecystectomy</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Knee arthroplasty</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Stent placement</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Spinal decompression</b>                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Implantable defibrillator insertion             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Shoulder arthroplasty                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary angioplasty                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| 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 arterial stent insertion               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic bypass                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder polypectomy                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carotid artery stent insertion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Bladder neoplasm surgery                        |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Transcatheter aortic valve implantation              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vocal cord augmentation                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Death  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 445 (0.00%) | 2 / 452 (0.44%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 2           | 0 / 1           |
| Chest pain   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Sudden death   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Sudden cardiac death                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Inflammation   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Fatigue  |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                            | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Reproductive system and breast disorders</b>        |                 |                 |                 |
| Cystocele  |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Prostatitis  |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Intermenstrual bleeding                                |                 |                 |                 |
| subjects affected / exposed                            | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                 |                 |                 |
| Acute respiratory failure                              |                 |                 |                 |
| subjects affected / exposed                            | 1 / 445 (0.22%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all        | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemoptysis  |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                                     |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory distress                                   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hydrothorax                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Sleep apnoea syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Alcoholism                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Conversion disorder                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Depression                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 445 (0.45%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Investigations                                  |                 |                 |                 |
| Angiogram cerebral                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Haemoglobin decreased                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Cardiovascular evaluation                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Sleep study                                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 445 (0.45%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Liver function test increased                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 445 (0.45%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Magnetic resonance imaging abnormal             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| SARS-CoV-2 test positive                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Fall  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 445 (0.45%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Concussion                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Carbon monoxide poisoning                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Femoral neck fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Foot fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Fibula fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Hand fracture                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Head injury                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 2 / 445 (0.45%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Humerus fracture                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Subdural haematoma                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Subcutaneous haematoma</b>                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Rib fracture</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Subdural haemorrhage</b>                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Traumatic fracture</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Tibia fracture</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Tendon rupture</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cervical vertebral fracture</b>              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Contusion</b>                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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 haemorrhage                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foreign body in gastrointestinal tract          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Congenital, familial and genetic disorders      |                 |                 |                 |
| Atrial septal defect                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 2 / 452 (0.44%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Aortic valve stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Angina unstable                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 3 / 445 (0.67%) | 3 / 452 (0.66%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 445 (0.45%) | 1 / 452 (0.22%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 2           |
| Bradycardia                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Atrioventricular block second degree            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block complete                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial flutter                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| 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 arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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 acute                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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 chronic                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chordae tendinae rupture                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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 disease                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 2 / 452 (0.44%) | 0 / 443 (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           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 2 / 452 (0.44%) | 3 / 443 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Myocardial ischaemia                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Palpitations                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| 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 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Supraventricular tachycardia                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intracardiac thrombus                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiopulmonary failure                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Acute coronary syndrome                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Sinus node dysfunction                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Amnesia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Brain stem infarction                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Carotid artery stenosis</b>                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cerebral artery occlusion</b>                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Cerebral haemorrhage</b>                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 2 / 2           |
| <b>Cerebral infarction</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 3 / 452 (0.66%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cerebral ischaemia</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cerebrovascular accident</b>                 |                 |                 |                 |
| subjects affected / exposed                     | 9 / 445 (2.02%) | 7 / 452 (1.55%) | 9 / 443 (2.03%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 8           | 0 / 10          |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| <b>Dizziness</b>                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Epilepsy</b>                                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive encephalopathy                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Headache  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic stroke                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           | 1 / 1           |
| Haemorrhagic cerebral infarction                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Facial paralysis                                |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Myasthenia gravis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Radiculopathy                                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 445 (0.22%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Syncope   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 445 (0.45%) | 0 / 452 (0.00%) | 0 / 443 (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                     | 4 / 445 (0.90%) | 4 / 452 (0.88%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar radiculopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Lacunar infarction                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhagic transformation stroke              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Stroke in evolution                             |                 |                 |                 |
| subjects affected / exposed                     | 3 / 445 (0.67%) | 3 / 452 (0.66%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic cerebral infarction                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic stroke                                |                 |                 |                 |

|   |                 |                  |                 |
|---|-----------------|------------------|-----------------|
| subjects affected / exposed                     | 9 / 445 (2.02%) | 13 / 452 (2.88%) | 9 / 443 (2.03%) |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 14           | 0 / 9           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 2           |
| <b>Motor dysfunction</b>                        |                 |                  |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%)  | 0 / 443 (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           |
| <b>Thrombotic cerebral infarction</b>           |                 |                  |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%)  | 0 / 443 (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           |
| <b>Carotid arteriosclerosis</b>                 |                 |                  |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%)  | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| <b>Brachial plexopathy</b>                      |                 |                  |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%)  | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| <b>Cerebral hypoperfusion</b>                   |                 |                  |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%)  | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| <b>Partial seizures</b>                         |                 |                  |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 2 / 452 (0.44%)  | 0 / 443 (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           |
| <b>Cerebral amyloid angiopathy</b>              |                 |                  |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%)  | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0            | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            | 0 / 0           |
| <b>Neurological decompensation</b>              |                 |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cerebral small vessel ischaemic disease</b>  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Cerebellar microhaemorrhage</b>              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Lacunar stroke</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hemianaesthesia</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |                 |
| <b>Anaemia</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Blood loss anaemia</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Iron deficiency anaemia</b>                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Thrombocytopenia</b>                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Ear and labyrinth disorders</b>              |                 |                 |                 |
| Vertigo   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Eye disorders</b>                            |                 |                 |                 |
| Macular oedema                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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 retinopathy                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cataract  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Retinal infarction                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Gastrointestinal disorders</b>               |                 |                 |                 |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Colitis ischaemic                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Duodenal ulcer haemorrhage                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dyspepsia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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 ulcer haemorrhage                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| Gastrointestinal haemorrhage                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Haematochezia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Inguinal hernia                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Intussusception                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Nausea</b>                                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Umbilical hernia</b>                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Stomach mass</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Paraesthesia oral</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Large intestine polyp</b>                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Mechanical ileus</b>                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hepatobiliary disorders</b>                  |                 |                 |                 |
| <b>Bile duct stone</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cholangitis acute</b>                        |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cholecystitis</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Hepatic failure</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hepatitis acute</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Drug-induced liver injury</b>                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cholecystitis acute</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Cholelithiasis</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Skin and subcutaneous tissue disorders</b>   |                 |                 |                 |
| <b>Angioedema</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Decubitus ulcer</b>                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin toxicity                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urticaria                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin ulcer                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Urinary retention                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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 kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 1 / 452 (0.22%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                            | 0 / 445 (0.00%) | 2 / 452 (0.44%) | 0 / 443 (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           |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |                 |                 |
| <b>Back pain</b>                                       |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 2 / 452 (0.44%) | 0 / 443 (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           |
| <b>Spinal pain</b>                                     |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Tenosynovitis</b>                                   |                 |                 |                 |
| subjects affected / exposed                            | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Pain in extremity</b>                               |                 |                 |                 |
| subjects affected / exposed                            | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Osteoporotic fracture</b>                           |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Infections and infestations</b>                     |                 |                 |                 |
| <b>Appendicitis</b>                                    |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastroenteritis</b>                                 |                 |                 |                 |
| subjects affected / exposed                            | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           | 0 / 1           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Diverticulitis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 3 / 445 (0.67%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia aspiration                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis acute                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| Septic shock                                    |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed  | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Staphylococcal sepsis</b>   |                 |                 |                 |
| subjects affected / exposed  | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all                      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Abdominal abscess</b>   |                 |                 |                 |
| subjects affected / exposed  | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all                      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all                           | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Joint abscess</b>   |                 |                 |                 |
| subjects affected / exposed  | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Infective exacerbation of chronic obstructive airways disease</b> |                 |                 |                 |
| subjects affected / exposed  | 0 / 445 (0.00%) | 1 / 452 (0.22%) | 0 / 443 (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           |
| <b>Pneumonia bacterial</b>   |                 |                 |                 |
| subjects affected / exposed  | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>COVID-19</b>  |                 |                 |                 |
| subjects affected / exposed  | 0 / 445 (0.00%) | 4 / 452 (0.88%) | 5 / 443 (1.13%) |
| occurrences causally related to treatment / all                      | 0 / 0           | 0 / 4           | 0 / 5           |
| deaths causally related to treatment / all                           | 0 / 0           | 0 / 0           | 0 / 1           |
| <b>COVID-19 pneumonia</b>  |                 |                 |                 |
| subjects affected / exposed  | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 2 / 443 (0.45%) |
| occurrences causally related to treatment / all                      | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all                           | 0 / 0           | 0 / 0           | 0 / 1           |
| <b>Metabolism and nutrition disorders</b>                            |                 |                 |                 |
| Hyperglycaemia   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 445 (0.22%) | 0 / 452 (0.00%) | 0 / 443 (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           |
| <b>Hyponatraemia</b>                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 445 (0.00%) | 0 / 452 (0.00%) | 1 / 443 (0.23%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>  | Asundexian 20 mg  |  |  |
|--|-------------------|--|--|
| <b>Total subjects affected by serious adverse events</b>                   |                   |  |  |
| subjects affected / exposed  | 83 / 446 (18.61%) |  |  |
| number of deaths (all causes)  | 6                 |  |  |
| number of deaths resulting from adverse events                             | 3                 |  |  |
| <b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b> |                   |  |  |
| <b>Gastric cancer</b>  |                   |  |  |
| subjects affected / exposed  | 1 / 446 (0.22%)   |  |  |
| occurrences causally related to treatment / all                            | 0 / 1             |  |  |
| deaths causally related to treatment / all                                 | 0 / 0             |  |  |
| <b>Endometrial adenocarcinoma</b>  |                   |  |  |
| subjects affected / exposed  | 0 / 446 (0.00%)   |  |  |
| occurrences causally related to treatment / all                            | 0 / 0             |  |  |
| deaths causally related to treatment / all                                 | 0 / 0             |  |  |
| <b>Glioblastoma multiforme</b>   |                   |  |  |
| subjects affected / exposed  | 0 / 446 (0.00%)   |  |  |
| occurrences causally related to treatment / all                            | 0 / 0             |  |  |
| deaths causally related to treatment / all                                 | 0 / 0             |  |  |
| <b>Metastases to central nervous system</b>                                |                   |  |  |
| subjects affected / exposed  | 0 / 446 (0.00%)   |  |  |
| occurrences causally related to treatment / all                            | 0 / 0             |  |  |
| deaths causally related to treatment / all                                 | 0 / 0             |  |  |
| <b>Lung neoplasm malignant</b>   |                   |  |  |
| subjects affected / exposed  | 0 / 446 (0.00%)   |  |  |
| occurrences causally related to treatment / all                            | 0 / 0             |  |  |
| deaths causally related to treatment / all                                 | 0 / 0             |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Lung cancer metastatic                          |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rectal cancer                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Oesophageal adenocarcinoma                      |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lung adenocarcinoma                             |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Prostate cancer                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Brain neoplasm                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Thymoma malignant                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Colorectal cancer                               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lung neoplasm                                   |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Metastasis</b>                               |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Invasive ductal breast carcinoma</b>         |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Vascular disorders</b>                       |                 |  |  |
| <b>Hypertensive crisis</b>                      |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hypertension</b>                             |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Aortic thrombosis</b>                        |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Peripheral ischaemia</b>                     |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Extremity necrosis</b>                       |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Deep vein thrombosis</b>                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Venous thrombosis                               |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombophlebitis                                |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atheroembolism                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Surgical and medical procedures                 |                 |  |  |
| Atrial septal defect repair                     |                 |  |  |
| subjects affected / exposed                     | 3 / 446 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac pacemaker insertion                     |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Carotid endarterectomy                          |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hip arthroplasty                                |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Endarterectomy                                  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coronary artery bypass                          |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholecystectomy                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Knee arthroplasty                               |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Stent placement                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal decompression                            |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Implantable defibrillator insertion             |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Shoulder arthroplasty                           |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coronary angioplasty                            |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Coronary arterial stent insertion                    |                 |  |  |
| subjects affected / exposed                          | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Aortic bypass  |                 |  |  |
| subjects affected / exposed                          | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Bladder polypectomy                                  |                 |  |  |
| subjects affected / exposed                          | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Carotid artery stent insertion                       |                 |  |  |
| subjects affected / exposed                          | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Bladder neoplasm surgery                             |                 |  |  |
| subjects affected / exposed                          | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Transcatheter aortic valve implantation              |                 |  |  |
| subjects affected / exposed                          | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Vocal cord augmentation                              |                 |  |  |
| subjects affected / exposed                          | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Death   |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Chest pain                                      |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sudden death                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sudden cardiac death                            |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Inflammation                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Fatigue   |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Reproductive system and breast disorders        |                 |  |  |
| Cystocele                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Prostatitis                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Intermenstrual bleeding                         |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory, thoracic and mediastinal disorders |                 |  |  |
| Acute respiratory failure                       |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemoptysis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory distress                            |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hydrothorax                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sleep apnoea syndrome                           |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Psychiatric disorders                           |                 |  |  |
| Alcoholism                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Conversion disorder                             |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Depression                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Angiogram cerebral                              |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemoglobin decreased                           |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiovascular evaluation                       |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sleep study                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Liver function test increased                   |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Magnetic resonance imaging abnormal             |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| SARS-CoV-2 test positive                        |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Fall  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Concussion                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Carbon monoxide poisoning                       |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Femoral neck fracture                           |                 |  |  |
| subjects affected / exposed                     | 2 / 446 (0.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Foot fracture                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Fibula fracture                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Femur fracture                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hand fracture                                   |                 |  |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Head injury                                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Hip fracture                                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Humerus fracture                                |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Subdural haematoma                              |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Subcutaneous haematoma                          |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Rib fracture                                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Subdural haemorrhage                            |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Traumatic fracture                              |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tibia fracture                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tendon rupture                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cervical vertebral fracture                     |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Contusion                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Post procedural haemorrhage                     |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lower limb fracture                             |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Foreign body in gastrointestinal tract          |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                       | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| <b>Congenital, familial and genetic disorders</b> |                 |  |  |
| Atrial septal defect                              |                 |  |  |
| subjects affected / exposed                       | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| <b>Cardiac disorders</b>                          |                 |  |  |
| Aortic valve stenosis                             |                 |  |  |
| subjects affected / exposed                       | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all   | 0 / 0           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Aortic valve incompetence                         |                 |  |  |
| subjects affected / exposed                       | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all   | 0 / 0           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Angina unstable                                   |                 |  |  |
| subjects affected / exposed                       | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all   | 0 / 0           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Angina pectoris                                   |                 |  |  |
| subjects affected / exposed                       | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all   | 0 / 1           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Atrial fibrillation                               |                 |  |  |
| subjects affected / exposed                       | 4 / 446 (0.90%) |  |  |
| occurrences causally related to treatment / all   | 0 / 4           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |
| Acute myocardial infarction                       |                 |  |  |
| subjects affected / exposed                       | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all   | 0 / 0           |  |  |
| deaths causally related to treatment / all        | 0 / 0           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Bradycardia                                     |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atrioventricular block second degree            |                 |  |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atrioventricular block complete                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Atrial flutter                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac arrest                                  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac failure                                 |                 |  |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac failure acute                           |                 |  |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Cardiac failure chronic                         |                 |  |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Cardiac failure congestive                      |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Chordae tendinae rupture</b>                 |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Coronary artery disease</b>                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Myocardial infarction</b>                    |                 |  |  |
| subjects affected / exposed                     | 2 / 446 (0.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Myocardial ischaemia</b>                     |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Palpitations</b>                             |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Pericardial effusion</b>                     |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Supraventricular tachycardia</b>             |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Intracardiac thrombus</b>                    |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cardiopulmonary failure</b>                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Acute coronary syndrome</b>                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Sinus node dysfunction</b>                   |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Nervous system disorders</b>                 |                 |  |  |
| <b>Amnesia</b>                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Brain stem infarction</b>                    |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Carotid artery stenosis</b>                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebral artery occlusion</b>                |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebral haemorrhage</b>                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebral infarction</b>                      |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebral ischaemia</b>                       |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebrovascular accident</b>                 |                 |  |  |
| subjects affected / exposed                     | 8 / 446 (1.79%) |  |  |
| occurrences causally related to treatment / all | 0 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Dizziness</b>                                |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Epilepsy</b>                                 |                 |  |  |
| subjects affected / exposed                     | 4 / 446 (0.90%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hypertensive encephalopathy</b>              |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Headache</b>                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Haemorrhagic stroke</b>                      |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhagic cerebral infarction                |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Facial paralysis                                |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myasthenia gravis                               |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Presyncope                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Radiculopathy                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Syncope   |                 |  |  |
| subjects affected / exposed                     | 3 / 446 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lumbar radiculopathy                            |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lacunar infarction                              |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhagic transformation stroke              |                 |  |  |
| subjects affected / exposed                     | 2 / 446 (0.45%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Stroke in evolution                             |                 |  |  |
| subjects affected / exposed                     | 4 / 446 (0.90%) |  |  |
| occurrences causally related to treatment / all | 0 / 4           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic cerebral infarction                   |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic stroke                                |                 |  |  |
| subjects affected / exposed                     | 7 / 446 (1.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 8           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Motor dysfunction                               |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombotic cerebral infarction                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Carotid arteriosclerosis                        |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Brachial plexopathy</b>                      |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebral hypoperfusion</b>                   |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Partial seizures</b>                         |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebral amyloid angiopathy</b>              |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Neurological decompensation</b>              |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebral small vessel ischaemic disease</b>  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cerebellar microhaemorrhage</b>              |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Lacunar stroke</b>                           |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hemianaesthesia</b>                          |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Blood and lymphatic system disorders</b>     |                 |  |  |
| <b>Anaemia</b>                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Blood loss anaemia</b>                       |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Iron deficiency anaemia</b>                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Thrombocytopenia</b>                         |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Ear and labyrinth disorders</b>              |                 |  |  |
| <b>Vertigo</b>                                  |                 |  |  |
| subjects affected / exposed                     | 3 / 446 (0.67%) |  |  |
| occurrences causally related to treatment / all | 0 / 3           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Eye disorders</b>                            |                 |  |  |
| <b>Macular oedema</b>                           |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Diabetic retinopathy                            |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cataract  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angle closure glaucoma                          |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Retinal infarction                              |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Colitis ischaemic                               |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Duodenal ulcer haemorrhage                      |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspepsia                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastric ulcer haemorrhage                       |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Gastrointestinal haemorrhage</b>             |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Haematochezia</b>                            |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Inguinal hernia</b>                          |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Intussusception</b>                          |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Melaena</b>                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Nausea</b>                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Umbilical hernia</b>                         |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Stomach mass</b>                             |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Paraesthesia oral</b>                        |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Large intestine polyp</b>                    |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Mechanical ileus</b>                         |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hepatobiliary disorders</b>                  |                 |  |  |
| <b>Bile duct stone</b>                          |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cholangitis acute</b>                        |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cholecystitis</b>                            |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hepatic failure</b>                          |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Hepatitis acute</b>                          |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Drug-induced liver injury</b>                |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cholecystitis acute</b>                      |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Cholelithiasis</b>                           |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Skin and subcutaneous tissue disorders</b>   |                 |  |  |
| <b>Angioedema</b>                               |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Decubitus ulcer</b>                          |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Skin toxicity</b>                            |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Urticaria</b>                                |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Skin ulcer</b>                               |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                            | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Renal and urinary disorders</b>                     |                 |  |  |
| Urinary retention                                      |                 |  |  |
| subjects affected / exposed                            | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Acute kidney injury                                    |                 |  |  |
| subjects affected / exposed                            | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Haematuria   |                 |  |  |
| subjects affected / exposed                            | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Nephrolithiasis  |                 |  |  |
| subjects affected / exposed                            | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Renal failure  |                 |  |  |
| subjects affected / exposed                            | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |  |  |
| Back pain  |                 |  |  |
| subjects affected / exposed                            | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Spinal pain  |                 |  |  |
| subjects affected / exposed                            | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all        | 0 / 0           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Tenosynovitis                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pain in extremity                               |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Osteoporotic fracture                           |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Appendicitis                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diverticulitis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cellulitis                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 446 (0.45%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia aspiration                            |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Pyelonephritis acute</b>                     |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Sepsis</b>                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| <b>Urosepsis</b>                                |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Urinary tract infection</b>                  |                 |  |  |
| subjects affected / exposed                     | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Septic shock</b>                             |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Staphylococcal sepsis</b>                    |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Abdominal abscess</b>                        |                 |  |  |
| subjects affected / exposed                     | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| <b>Joint abscess</b>                            |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                                   | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all               | 0 / 0           |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |
| Infective exacerbation of chronic obstructive airways disease |                 |  |  |
| subjects affected / exposed                                   | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all               | 0 / 0           |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |
| Pneumonia bacterial   |                 |  |  |
| subjects affected / exposed                                   | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all               | 0 / 0           |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |
| COVID-19  |                 |  |  |
| subjects affected / exposed                                   | 1 / 446 (0.22%) |  |  |
| occurrences causally related to treatment / all               | 0 / 1           |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |
| COVID-19 pneumonia  |                 |  |  |
| subjects affected / exposed                                   | 3 / 446 (0.67%) |  |  |
| occurrences causally related to treatment / all               | 0 / 3           |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |
| Metabolism and nutrition disorders                            |                 |  |  |
| Hyperglycaemia  |                 |  |  |
| subjects affected / exposed                                   | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all               | 0 / 0           |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |
| Hyponatraemia   |                 |  |  |
| subjects affected / exposed                                   | 0 / 446 (0.00%) |  |  |
| occurrences causally related to treatment / all               | 0 / 0           |  |  |
| deaths causally related to treatment / all                    | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>   | Asundexian 10 mg                                     | Placebo  | Asundexian 50 mg                                     |
|---|--|--|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed  | 126 / 445 (28.31%)                                   | 136 / 452 (30.09%)                                   | 136 / 443 (30.70%)                                   |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)  | 23 / 445 (5.17%)<br>24                               | 24 / 452 (5.31%)<br>25                               | 25 / 443 (5.64%)<br>25                               |
| Cardiac disorders<br>Atrial fibrillation<br>subjects affected / exposed<br>occurrences (all)  | 18 / 445 (4.04%)<br>18                               | 22 / 452 (4.87%)<br>22                               | 16 / 443 (3.61%)<br>16                               |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)       | 7 / 445 (1.57%)<br>7<br><br>19 / 445 (4.27%)<br>20   | 14 / 452 (3.10%)<br>14<br><br>18 / 452 (3.98%)<br>19 | 17 / 443 (3.84%)<br>17<br><br>21 / 443 (4.74%)<br>31 |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 28 / 445 (6.29%)<br>29<br><br>12 / 445 (2.70%)<br>12 | 34 / 452 (7.52%)<br>35<br><br>12 / 452 (2.65%)<br>12 | 28 / 443 (6.32%)<br>29<br><br>15 / 443 (3.39%)<br>18 |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 6 / 445 (1.35%)<br>6                                 | 12 / 452 (2.65%)<br>13                               | 11 / 443 (2.48%)<br>12                               |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 11 / 445 (2.47%)<br>11                               | 12 / 452 (2.65%)<br>12                               | 16 / 443 (3.61%)<br>16                               |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)<br><br>COVID-19  | 13 / 445 (2.92%)<br>15                               | 14 / 452 (3.10%)<br>18                               | 13 / 443 (2.93%)<br>14                               |

|                             |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 22 / 445 (4.94%) | 12 / 452 (2.65%) | 14 / 443 (3.16%) |
| occurrences (all)           | 22               | 12               | 14               |

|   |                    |  |  |
|---|--------------------|--|--|
| <b>Non-serious adverse events</b>                     | Asundexian 20 mg   |  |  |
| Total subjects affected by non-serious adverse events |                    |  |  |
| subjects affected / exposed                           | 127 / 446 (28.48%) |  |  |
| Vascular disorders                                    |                    |  |  |
| Hypertension  |                    |  |  |
| subjects affected / exposed                           | 19 / 446 (4.26%)   |  |  |
| occurrences (all)                                     | 19                 |  |  |
| Cardiac disorders                                     |                    |  |  |
| Atrial fibrillation                                   |                    |  |  |
| subjects affected / exposed                           | 21 / 446 (4.71%)   |  |  |
| occurrences (all)                                     | 21                 |  |  |
| Nervous system disorders                              |                    |  |  |
| Dizziness   |                    |  |  |
| subjects affected / exposed                           | 16 / 446 (3.59%)   |  |  |
| occurrences (all)                                     | 18                 |  |  |
| Headache  |                    |  |  |
| subjects affected / exposed                           | 19 / 446 (4.26%)   |  |  |
| occurrences (all)                                     | 38                 |  |  |
| Gastrointestinal disorders                            |                    |  |  |
| Constipation  |                    |  |  |
| subjects affected / exposed                           | 18 / 446 (4.04%)   |  |  |
| occurrences (all)                                     | 20                 |  |  |
| Diarrhoea   |                    |  |  |
| subjects affected / exposed                           | 14 / 446 (3.14%)   |  |  |
| occurrences (all)                                     | 15                 |  |  |
| Psychiatric disorders                                 |                    |  |  |
| Insomnia  |                    |  |  |
| subjects affected / exposed                           | 16 / 446 (3.59%)   |  |  |
| occurrences (all)                                     | 16                 |  |  |
| Musculoskeletal and connective tissue disorders       |                    |  |  |
| Arthralgia  |                    |  |  |
| subjects affected / exposed                           | 11 / 446 (2.47%)   |  |  |
| occurrences (all)                                     | 13                 |  |  |
| Infections and infestations                           |                    |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all) | 11 / 446 (2.47%)<br>11 |  |  |
| COVID-19<br>subjects affected / exposed<br>occurrences (all)                | 14 / 446 (3.14%)<br>14 |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/36063821>