



Clinical trial results:

Long term single-arm open-label study, to assess the safety and tolerability of selexipag

(ACT-293987) in patients with pulmonary arterial hypertension

Summary

| | |
|--------------------------|---|
| EudraCT number | 2009-014992-31 |
| Trial protocol | BE FR ES SE DK GB IE PL AT HU DE SK CZ GR NL IT |
| Global end of trial date | 29 September 2021 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 09 September 2022 |
| First version publication date | 09 September 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | AC-065A303 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01112306 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Actelion Pharmaceuticals Ltd |
| Sponsor organisation address | Gewerbestrasse 16, Allschwil, Switzerland, 4123 |
| Public contact | Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.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 | 29 September 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 September 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess long-term safety and tolerability of selexipag in subjects with pulmonary arterial hypertension (PAH).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 15 June 2010 |
| 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 | Argentina: 20 |
| Country: Number of subjects enrolled | Australia: 37 |
| Country: Number of subjects enrolled | Austria: 3 |
| Country: Number of subjects enrolled | Belgium: 17 |
| Country: Number of subjects enrolled | Belarus: 34 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Country: Number of subjects enrolled | Chile: 31 |
| Country: Number of subjects enrolled | China: 113 |
| Country: Number of subjects enrolled | Colombia: 3 |
| Country: Number of subjects enrolled | Czechia: 11 |
| Country: Number of subjects enrolled | Germany: 35 |
| Country: Number of subjects enrolled | Denmark: 4 |
| Country: Number of subjects enrolled | Spain: 8 |
| Country: Number of subjects enrolled | France: 21 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Greece: 6 |
| Country: Number of subjects enrolled | Hungary: 10 |
| Country: Number of subjects enrolled | India: 15 |
| Country: Number of subjects enrolled | Ireland: 4 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Israel: 11 |
| Country: Number of subjects enrolled | Italy: 4 |
| Country: Number of subjects enrolled | Korea, Republic of: 11 |
| Country: Number of subjects enrolled | Mexico: 20 |
| Country: Number of subjects enrolled | Malaysia: 2 |
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Peru: 6 |
| Country: Number of subjects enrolled | Poland: 7 |
| Country: Number of subjects enrolled | Romania: 9 |
| Country: Number of subjects enrolled | Russian Federation: 72 |
| Country: Number of subjects enrolled | Singapore: 8 |
| Country: Number of subjects enrolled | Serbia: 10 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | Sweden: 10 |
| Country: Number of subjects enrolled | Thailand: 4 |
| Country: Number of subjects enrolled | Turkey: 8 |
| Country: Number of subjects enrolled | Taiwan: 11 |
| Country: Number of subjects enrolled | Ukraine: 35 |
| Country: Number of subjects enrolled | United States: 80 |
| Worldwide total number of subjects | 709 |
| EEA total number of subjects | 154 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 597 |
| From 65 to 84 years | 112 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 709 subjects were enrolled in the study. Out of the 709 subjects, 424 subjects completed the study.

Period 1

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

Arms

| | |
|-----------|-----------|
| Arm title | Selexipag |
|-----------|-----------|

Arm description:

Subjects with pulmonary arterial hypertension (PAH) who completed the double-blind AC-065A302 GRIPHON study or experienced a morbidity/mortality event in that study, entered in this open label (OL) study. Subjects who received selexipag in GRIPHON continued to receive selexipag at the same dose (200 micrograms [mcg], twice daily [bid] up to 1600 mcg bid based on individual maximum tolerated dose) in this OL study. Subjects who were on placebo or experienced a morbidity/mortality event in GRIPHON entered the titration period of this OL-study and received lowest dose of selexipag (200 mcg, bid) and dose was titrated up to 1600 mcg bid, based on the individual maximum tolerated dose. Each subject received study drug from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).

| | |
|--|-------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Selexipag |
| Investigational medicinal product code | |
| Other name | JNJ-67896049 ACT-293987 |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Selexipag (up-titrated from 200 mcg bid to 1600 mcg bid based on individual maximum tolerated dose) was administered bid with food from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).

| Number of subjects in period 1 | Selexipag |
|--------------------------------|-----------|
| Started | 709 |
| Completed | 424 |
| Not completed | 285 |
| Adverse event, serious fatal | 175 |
| Consent withdrawn by subject | 31 |
| Unspecified | 70 |
| Lost to follow-up | 9 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Selexipag |
|-----------------------|-----------|

Reporting group description:

Subjects with pulmonary arterial hypertension (PAH) who completed the double-blind AC-065A302 GRIPHON study or experienced a morbidity/mortality event in that study, entered in this open label (OL) study. Subjects who received selexipag in GRIPHON continued to receive selexipag at the same dose (200 micrograms [mcg], twice daily [bid] up to 1600 mcg bid based on individual maximum tolerated dose) in this OL study. Subjects who were on placebo or experienced a morbidity/mortality event in GRIPHON entered the titration period of this OL-study and received lowest dose of selexipag (200 mcg, bid) and dose was titrated up to 1600 mcg bid, based on the individual maximum tolerated dose. Each subject received study drug from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).

| Reporting group values | Selexipag | Total | |
|---|-----------|-------|--|
| Number of subjects | 709 | 709 | |
| Title for AgeCategorical Units: subjects | | | |
| Adolescents: 12-<18 yrs | 0 | 0 | |
| Adults: >= 18 yrs | 709 | 709 | |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 47.9 | | |
| standard deviation | ± 15.19 | - | |
| Title for Gender Units: subjects | | | |
| Female | 590 | 590 | |
| Male | 119 | 119 | |

End points

End points reporting groups

| | |
|--|-----------|
| Reporting group title | Selexipag |
| Reporting group description: | |
| Subjects with pulmonary arterial hypertension (PAH) who completed the double-blind AC-065A302 GRIPHON study or experienced a morbidity/mortality event in that study, entered in this open label (OL) study. Subjects who received selexipag in GRIPHON continued to receive selexipag at the same dose (200 micrograms [mcg], twice daily [bid] up to 1600 mcg bid based on individual maximum tolerated dose) in this OL study. Subjects who were on placebo or experienced a morbidity/mortality event in GRIPHON entered the titration period of this OL-study and received lowest dose of selexipag (200 mcg, bid) and dose was titrated up to 1600 mcg bid, based on the individual maximum tolerated dose. Each subject received study drug from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years). | |

Primary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs) up to 3 days After Study Intervention Discontinuation

| | |
|-----------------|--|
| End point title | Number of Subjects with Treatment-emergent Adverse Events (TEAEs) up to 3 days After Study Intervention Discontinuation ^[1] |
|-----------------|--|

End point description:

An adverse event (AE) is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. A TEAE is any AE temporally associated with the use of study drug (from study drug initiation until 3 days after study drug discontinuation), whether or not considered related to the study drug. The safety set included all randomised subjects who received at least 1 dose of selexipag or placebo.

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

End point timeframe:

Up to 3 days after drug discontinuation (Up to 10.5 years)

Notes:

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

Justification: No inferential statistics was planned for this primary endpoint.

| End point values | Selexipag | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 709 | | | |
| Units: subjects | 684 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with TEAEs Leading to Permanent Discontinuation of Study Intervention

| | |
|-----------------|---|
| End point title | Number of Subjects with TEAEs Leading to Permanent Discontinuation of Study Intervention ^[2] |
|-----------------|---|

End point description:

An adverse event (AE) is any untoward medical event that occurs in a subject administered an

investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. A TEAE is any AE temporally associated with the use of study drug (from study drug initiation until 3 days after study drug discontinuation), whether or not considered related to the study drug. The safety set included all randomised subjects who received at least 1 dose of selexipag or placebo.

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

End point timeframe:

Up to 10.5 years

Notes:

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

Justification: No inferential statistics was planned for this primary endpoint.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Selexipag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 709 | | | |
| Units: subjects | 129 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Serious Adverse Events (TESAEs) up to 3 days After Study Intervention Discontinuation

| | |
|-----------------|---|
| End point title | Number of Subjects with Treatment-emergent Serious Adverse Events (TESAEs) up to 3 days After Study Intervention Discontinuation ^[3] |
|-----------------|---|

End point description:

An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. SAE is any AE that results in: death, persistent or significant disability/incapacity, requires inpatient hospitalisation or prolongation of existing hospitalisation, is life-threatening experience, is a congenital anomaly/birth defect and may jeopardise subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above. Those SAEs occurring during study drug administration, that is, between study drug initiation and three days after study drug discontinuation, are defined as treatment-emergent SAEs. The safety set included all randomised subjects who received at least 1 dose of selexipag or placebo.

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

End point timeframe:

Up to 3 days after drug discontinuation (Up to 10.5 years)

Notes:

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

Justification: No inferential statistics was planned for this primary endpoint.

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Selexipag | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 709 | | | |
| Units: subjects | 420 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 10.5 years for serious and other (non-serious) adverse events and up to 11.2 years for all-cause mortality

Adverse event reporting additional description:

The safety set included all randomised subjects who received at least 1 dose of selexipag or placebo.

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

Dictionary used

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

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|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Selexipag |
|-----------------------|-----------|

Reporting group description:

Subjects with pulmonary arterial hypertension (PAH) who completed the double-blind AC-065A302 GRIPHON study or experienced a morbidity/mortality event in that study, entered in this open label (OL) study. Subjects who received selexipag in GRIPHON continued to receive selexipag at the same dose (200 micrograms [mcg], twice daily [bid] up to 1600 mcg bid based on individual maximum tolerated dose) in this OL study. Subjects who were on placebo or experienced a morbidity/mortality event in GRIPHON entered the titration period of this OL-study and received lowest dose of selexipag (200 mcg, bid) and dose was titrated up to 1600 mcg bid, based on the individual maximum tolerated dose. Each subject received study drug from Day 1 until the earliest of a) selexipag became commercially available in this indication in subject's country, b) sponsor decided to stop current study, or c) subject/investigator decided to discontinue study intervention (up to 10.5 years).

| Serious adverse events | Selexipag | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 420 / 709 (59.24%) | | |
| number of deaths (all causes) | 186 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma of Colon | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Benign Salivary Gland Neoplasm | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast Cancer Metastatic | | | |

| | | | | |
|--|-----------------|--|--|--|
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Breast Cancer Recurrent | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Carcinoid Tumour of the Stomach | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endometrial Cancer Stage I | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endometrial Adenocarcinoma | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Extranodal Marginal Zone B-Cell Lymphoma (Malt Type) | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infected Neoplasm | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatocellular Carcinoma | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Lung Adenocarcinoma | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung Neoplasm Malignant | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metastases to the Mediastinum | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nodal Marginal Zone B-Cell Lymphoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Ovarian Germ Cell Teratoma Benign | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Papillary Thyroid Cancer | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine Leiomyoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Circulatory Collapse | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Deep Vein Thrombosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypotension | | | |
| subjects affected / exposed | 6 / 709 (0.85%) | | |
| occurrences causally related to treatment / all | 1 / 6 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypovolaemic Shock | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 1 / 1 | | |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral Ischaemia | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral Arterial Occlusive Disease | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vasculitis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Superior Vena Cava Perforation | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Venous Thrombosis Limb | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Benign Breast Lump Removal | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Balloon Atrial Septostomy | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Breast Conserving Surgery | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary Arterial Stent Insertion | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug Therapy | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac Pacemaker Insertion | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coronary Angioplasty | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric Bypass | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fasciotomy | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Heart and Lung Transplant | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hip Arthroplasty | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Knee Operation | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lung Transplant | | | | |
| subjects affected / exposed | 5 / 709 (0.71%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nephrectomy | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ovarian Cystectomy | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Packed Red Blood Cell Transfusion | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rehabilitation Therapy | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Percutaneous Coronary Intervention | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transfusion | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicose Vein Operation | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular Operation | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Abortion Missed | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy | | | |
| subjects affected / exposed | 5 / 709 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abortion Spontaneous | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Catheter Site Erythema | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Catheter Site Thrombosis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chest Discomfort | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Chest Pain | | | |
| subjects affected / exposed | 7 / 709 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Drowning | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Drug Interaction | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug Ineffective | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Euthanasia | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Gait Disturbance | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fatigue | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Generalised Oedema | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Multiple Organ Dysfunction Syndrome | | | | |
| subjects affected / exposed | 8 / 709 (1.13%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 7 | | | |
| Oedema Peripheral | | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Peripheral Swelling | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Organ Failure | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 709 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sudden Cardiac Death | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Sudden Death | | | |
| subjects affected / exposed | 14 / 709 (1.97%) | | |
| occurrences causally related to treatment / all | 0 / 14 | | |
| deaths causally related to treatment / all | 0 / 14 | | |
| Systemic Inflammatory Response Syndrome | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Withdrawal Syndrome | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Immune system disorders | | | |
| Amyloidosis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| Uterine Haemorrhage | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vaginal Haemorrhage | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute Pulmonary Oedema | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute Respiratory Failure | | | |
| subjects affected / exposed | 5 / 709 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic Respiratory Failure | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 18 / 709 (2.54%) | | |
| occurrences causally related to treatment / all | 0 / 21 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|------------------|--|--|--|
| Dyspnoea Exertional | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemoptysis | | | | |
| subjects affected / exposed | 10 / 709 (1.41%) | | | |
| occurrences causally related to treatment / all | 1 / 13 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epistaxis | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypersensitivity Pneumonitis | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower Respiratory Tract Inflammation | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoxia | | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lupus Pneumonitis | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleuritic Pain | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pleurisy | | | | |

| | | | |
|---|--------------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary Alveolar Haemorrhage | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary Arterial Hypertension | | | |
| subjects affected / exposed | 169 / 709 (23.84%) | | |
| occurrences causally related to treatment / all | 2 / 220 | | |
| deaths causally related to treatment / all | 1 / 66 | | |
| Pulmonary Artery Dilatation | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary Artery Aneurysm | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 8 / 709 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 12 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Pulmonary Hypertension | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pulmonary Oedema | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pulmonary Mass | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory Distress | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory Failure | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Psychiatric disorders | | | |
| Acute Psychosis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Drug Dependence | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Major Depression | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Suicide Attempt | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |

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|---|-----------------|--|--|--|
| Bile Duct Stone | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cholecystitis | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cardiac Cirrhosis | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cholecystitis Acute | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cirrhosis Alcoholic | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cholelithiasis | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Drug-Induced Liver Injury | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic Failure | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Jaundice | | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Activated Partial Thromboplastin Time Prolonged | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anticoagulation Drug Level above Therapeutic | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood Uric Acid Increased | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Biopsy Kidney | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Catheterisation Cardiac | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemoglobin Decreased | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| International Normalised Ratio Increased | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|-----------------|--|--|--|
| Investigation | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| N-Terminal Prohormone Brain Natriuretic Peptide Increased | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Precancerous Cells Present | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transplant Evaluation | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Prothrombin Time Prolonged | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Weight Decreased | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 1 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury, poisoning and procedural complications | | | | |
| Accident | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Anaesthetic Complication | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |

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|---|-----------------|--|--|--|
| Ankle Fracture | | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fall | | | | |
| subjects affected / exposed | 8 / 709 (1.13%) | | | |
| occurrences causally related to treatment / all | 0 / 8 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Contusion | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Concussion | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Head Injury | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fractured Sacrum | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Femoral Neck Fracture | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Humerus Fracture | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intentional Overdose | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Jaw Fracture | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Joint Dislocation | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Overdose | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pelvic Fracture | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Poisoning | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Radius Fracture | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post Procedural Haemorrhage | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Reactive Gastropathy | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road Traffic Accident | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rib Fracture | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin Laceration | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Soft Tissue Injury | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal Compression Fracture | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subcutaneous Haematoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Spinal Fracture | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Toxicity to Various Agents | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Traumatic Haematoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper Limb Fracture | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular Pseudoaneurysm | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Congenital, familial and genetic disorders | | | |
| Dermoid Cyst | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic Arteriovenous Malformation | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Acute Coronary Syndrome | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 2 | | |

| | | | | |
|---|------------------|--|--|--|
| Acute Right Ventricular Failure | | | | |
| subjects affected / exposed | 11 / 709 (1.55%) | | | |
| occurrences causally related to treatment / all | 0 / 11 | | | |
| deaths causally related to treatment / all | 0 / 11 | | | |
| Angina Pectoris | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Aortic Valve Stenosis | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Arrhythmia | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial Fibrillation | | | | |
| subjects affected / exposed | 17 / 709 (2.40%) | | | |
| occurrences causally related to treatment / all | 0 / 23 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial Tachycardia | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrial Flutter | | | | |
| subjects affected / exposed | 8 / 709 (1.13%) | | | |
| occurrences causally related to treatment / all | 0 / 10 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Atrioventricular Block | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Atrioventricular Block Second Degree | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular Block Complete | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac Arrest | | | |
| subjects affected / exposed | 13 / 709 (1.83%) | | |
| occurrences causally related to treatment / all | 0 / 13 | | |
| deaths causally related to treatment / all | 0 / 13 | | |
| Cardiac Failure | | | |
| subjects affected / exposed | 8 / 709 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 12 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Cardiac Failure Acute | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Cardiac Failure Chronic | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiopulmonary Failure | | | |
| subjects affected / exposed | 8 / 709 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 8 | | |
| Cardiogenic Shock | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 9 / 709 (1.27%) | | |
| occurrences causally related to treatment / all | 0 / 9 | | |
| deaths causally related to treatment / all | 0 / 8 | | |
| Cardio-Respiratory Arrest | | | |
| subjects affected / exposed | 5 / 709 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 5 | | |
| Cardiorenal Syndrome | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiovascular Insufficiency | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Chronic Left Ventricular Failure | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic Right Ventricular Failure | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cor Pulmonale | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cor Pulmonale Acute | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial Infarction | | | |

| | | | |
|---|-------------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Left Ventricular Failure | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Coronary Artery Disease | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pericardial Effusion | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Right Ventricular Dysfunction | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Right Ventricular Failure | | | |
| subjects affected / exposed | 93 / 709 (13.12%) | | |
| occurrences causally related to treatment / all | 1 / 163 | | |
| deaths causally related to treatment / all | 0 / 39 | | |
| Supraventricular Tachycardia | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Tricuspid Valve Incompetence | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular Tachyarrhythmia | | | |

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|---|-----------------|--|--|
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebral Infarction | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Carotid Artery Occlusion | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intracranial Haematoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic Stroke | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 18 / 709 (2.54%) | | |
| occurrences causally related to treatment / all | 0 / 25 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vocal Cord Paralysis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Transient Ischaemic Attack | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 9 / 709 (1.27%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Anaemia Vitamin B12 Deficiency | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bone Marrow Failure | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood Loss Anaemia | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Disseminated Intravascular Coagulation | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Immune Thrombocytopenic Purpura | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Iron Deficiency Anaemia | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pseudolymphoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphadenopathy Mediastinal | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |

| | | | |
|---|-----------------|--|--|
| Diabetic Retinopathy | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Astigmatism | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal Distension | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal Hernia | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 1 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal Wall Haematoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abdominal Pain Lower | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Chronic Gastritis | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites | | | |
| subjects affected / exposed | 6 / 709 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 9 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Colitis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 12 / 709 (1.69%) | | |
| occurrences causally related to treatment / all | 3 / 13 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diverticular Perforation | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis Haemorrhagic | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastric Ulcer | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 9 / 709 (1.27%) | | |
| occurrences causally related to treatment / all | 0 / 9 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Gastrointestinal Motility Disorder | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus Paralytic | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large Intestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Large Intestine Polyp | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Melaena | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstructive Pancreatitis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oesophageal Haemorrhage | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis Acute | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal Haemorrhage | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Skin Necrosis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin Ulcer | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Chronic Kidney Disease | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 6 / 709 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 8 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cystitis Haemorrhagic | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glomerulonephritis Chronic | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ischaemic Nephropathy | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematuria | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lupus Nephritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal Failure | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proteinuria | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal Haematoma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tubulointerstitial Nephritis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal Impairment | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary Retention | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Adrenocortical Insufficiency Acute | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Basedow's Disease | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thyroiditis Subacute | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back Pain | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fracture Malunion | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mixed Connective Tissue Disease | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematoma Muscle | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neck Pain | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rheumatoid Arthritis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Systemic Lupus Erythematosus | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Still's Disease | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 6 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Systemic Scleroderma | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess Bacterial | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Abscess Limb | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Appendicitis | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anal Abscess | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Actinomycotic Pulmonary Infection | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterial Abdominal Infection | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Atypical Pneumonia | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Appendicitis Perforated | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Bacterial Sepsis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Bronchitis | | | |
| subjects affected / exposed | 11 / 709 (1.55%) | | |
| occurrences causally related to treatment / all | 0 / 13 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 6 / 709 (0.85%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium Difficile Colitis | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Colonic Abscess | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cystitis | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Corona Virus Infection | | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | | |
| occurrences causally related to treatment / all | 0 / 5 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Complicated Appendicitis | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dengue Fever | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Disseminated Tuberculosis | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Empyema | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Endocarditis | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Enterobacter Sepsis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Erysipelas | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia Sepsis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Escherichia Urinary Tract Infection | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis Norovirus | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis Clostridial | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal Infection | | | |

| | | | | |
|---|-----------------|--|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| H1n1 Influenza | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpes Zoster | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haemorrhagic Pneumonia | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Haematoma Infection | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infective Tenosynovitis | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection | | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Influenza | | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower Respiratory Tract Infection | | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 8 / 709 (1.13%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lung Infection | | | |
| subjects affected / exposed | 5 / 709 (0.71%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis Media Bacterial | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis Bacterial | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 2 | | |
| Pneumonia | | | |
| subjects affected / exposed | 50 / 709 (7.05%) | | |
| occurrences causally related to treatment / all | 0 / 58 | | |
| deaths causally related to treatment / all | 0 / 10 | | |
| Pneumonia Bacterial | | | |

| | | | |
|---|------------------|--|--|
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pneumonia Viral | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Postoperative Wound Infection | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyelonephritis Acute | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyoderma | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Sepsis | | | |
| subjects affected / exposed | 10 / 709 (1.41%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 4 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory Tract Infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 7 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Septic Shock | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 3 | | |
| Sialoadenitis | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Soft Tissue Infection | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Staphylococcal Sepsis | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 2 / 709 (0.28%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 4 / 709 (0.56%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral Infection | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound Infection | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Fluid Overload | | | |
| subjects affected / exposed | 3 / 709 (0.42%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fluid Retention | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypoproteinaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 709 (0.14%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Selexipag | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 598 / 709 (84.34%) | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 49 / 709 (6.91%) | | |
| occurrences (all) | 54 | | |
| Hypotension | | | |
| subjects affected / exposed | 38 / 709 (5.36%) | | |
| occurrences (all) | 48 | | |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 43 / 709 (6.06%) | | |
| occurrences (all) | 48 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 71 / 709 (10.01%) | | |
| occurrences (all) | 88 | | |
| Headache | | | |
| subjects affected / exposed | 328 / 709 (46.26%) | | |
| occurrences (all) | 469 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 65 / 709 (9.17%) | | |
| occurrences (all) | 78 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 44 / 709 (6.21%) | | |
| occurrences (all) | 48 | | |
| Oedema Peripheral | | | |

| | | | |
|---|--------------------|--|--|
| subjects affected / exposed | 90 / 709 (12.69%) | | |
| occurrences (all) | 104 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 209 / 709 (29.48%) | | |
| occurrences (all) | 274 | | |
| Nausea | | | |
| subjects affected / exposed | 135 / 709 (19.04%) | | |
| occurrences (all) | 171 | | |
| Vomiting | | | |
| subjects affected / exposed | 74 / 709 (10.44%) | | |
| occurrences (all) | 90 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 80 / 709 (11.28%) | | |
| occurrences (all) | 96 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 76 / 709 (10.72%) | | |
| occurrences (all) | 99 | | |
| Pulmonary Arterial Hypertension | | | |
| subjects affected / exposed | 68 / 709 (9.59%) | | |
| occurrences (all) | 77 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 65 / 709 (9.17%) | | |
| occurrences (all) | 75 | | |
| Myalgia | | | |
| subjects affected / exposed | 68 / 709 (9.59%) | | |
| occurrences (all) | 92 | | |
| Pain in Extremity | | | |
| subjects affected / exposed | 78 / 709 (11.00%) | | |
| occurrences (all) | 97 | | |
| Pain in Jaw | | | |
| subjects affected / exposed | 130 / 709 (18.34%) | | |
| occurrences (all) | 153 | | |
| Infections and infestations | | | |

| | | | |
|------------------------------------|-------------------|--|--|
| Bronchitis | | | |
| subjects affected / exposed | 59 / 709 (8.32%) | | |
| occurrences (all) | 76 | | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 42 / 709 (5.92%) | | |
| occurrences (all) | 54 | | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 84 / 709 (11.85%) | | |
| occurrences (all) | 130 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 88 / 709 (12.41%) | | |
| occurrences (all) | 125 | | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 44 / 709 (6.21%) | | |
| occurrences (all) | 54 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 19 March 2010 | The purpose of this amendment was: the double-blind studies AC-065A301 and AC-065A302 (2009-014490-41) were merged into a single study and all references were replaced by the reference to the merged protocol AC-065A302; subjects who experienced a Critical Event Committee (CEC)-confirmed clinical worsening event during study AC-065A302 could only enter study AC-065A303 after their Week 16 visit of study AC-065A302 and after written approval from the sponsor. These restrictions were removed; a time limit of 2 weeks after the last visit in study AC-065A302 was introduced for entering study AC-065A303; and clarification that prostacyclin and prostanoid therapy were prohibited not only during study AC-065A303 but also during the transition period between study AC-065A302 and study AC-065A303. |
| 20 December 2010 | The purpose of this amendment was: the precautionary wording regarding sun exposure was removed and the Independent Data Monitoring Committee reviewing unblinded safety data of Study AC-065A302 was also assigned the review of safety data from the study AC-065A303. |
| 19 April 2013 | The purpose of this amendment was: sample size was increased from 670 up to a maximum of 1150 and collection of safety data in the clinical database was extended to vital signs, body weight, concomitant medications, and laboratory results; guidance for management of subjects with liver impairment was provided; and eligibility of study AC-065A302 subjects to study AC-065A303 was extended to subjects with worsening of pulmonary arterial hypertension (PAH) during the treatment extension period of study AC-065A302. |
| 16 March 2015 | The purpose of this amendment was: the possibility to up-titrate selexipag at unscheduled visits (for subjects who had not reached the maximum allowed dose) was introduced; the overall duration of study AC-065A303 was changed from "until the approval of selexipag in PAH" to "until selexipag is commercially available"; temporary concomitant use of selexipag and intravenous (IV), subcutaneous (SC), or inhaled prostacyclin and prostacyclin analogs was allowed when deemed medically indicated for the subject; and a discontinuation criterion for subjects diagnosed with pulmonary venoocclusive disease (PVOD) was introduced. |
| 15 June 2016 | The purpose of this amendment was: disbandment of the Data Monitoring Committee involved in study AC-065A302 and Ophthalmology Safety Board as of 01 July 2016; and the reference to the selexipag Investigator Brochure (IB) Section 6 was replaced with the complete list of adverse events. |
| 25 January 2017 | The purpose of this amendment was: further to new drug-drug interaction study results, concomitant administration of strong cytochrome P450 (CYP)2C8 inhibitors such as gemfibrozil was to be avoided and in case of concomitant administration of rifampicin, dose adjustment of selexipag could be required. |
| 30 June 2017 | The purpose of this amendment was to: contraindication of strong CYP2C8 inhibitors such as gemfibrozil in accordance with IB Version 11 was added; and information on the lack of studies to determine the effect of moderate inhibitors of CYP2C8, and strong inhibitors of UGT1A3 and UGT2B7 on the exposure to selexipag or its active metabolite was added. |

| | |
|------------------|--|
| 06 February 2019 | The purpose of this amendment was: Guidance for concomitant administration of selexipag and moderate inhibitors of CYP2C8 was updated based on Phase 1 study AC-065-117, in accordance with IB Version 13; clinical information section was updated to include reference to the recently completed studies along with the results in accordance with IB Version 13; statistical section was updated according to International Council for Harmonisation E6 guideline; and the data collection section was updated to allow the use of a standard ballpoint pen to complete the Case Report Forms (CRF). |
|------------------|--|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The open-label, uncontrolled design, additional PAH-specific treatments in limited subjects for limited time, a variable study duration due to commercial selexipag availability and limitation of safety data reporting in China by 20-Dec-2019.

Notes: