# Clinical trial results:
# A multicenter, randomized, double-blind, placebo-controlled study to demonstrate that digitoxin reduces a composite of overall mortality and hospitalization for worsening heart failure in patients with chronic heart failure and reduced ejection fraction

## Summary

| | |
|---|---|
| EudraCT number | 2013-005326-38 |
| Trial protocol | DE AT |
| Global end of trial date | 29 November 2024 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 26 February 2026 |
| First version publication date | 26 February 2026 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | DIGIT-HF |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Hannover Medical School |
| Sponsor organisation address | Carl-Neuberg-Str. 1, Hannover, Germany, 30625 |
| Public contact | Stabsstelle Zentrum für Klinische Studien, Hannover Medical School, EudraCT@mh-hannover.de |
| Scientific contact | Stabsstelle Zentrum für Klinische Studien, Hannover Medical School, EudraCT@mh-hannover.de |

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 | 24 November 2025 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 29 November 2024 |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 November 2024 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate in a large and simple clinical trial-approach that digitoxin (target serum concentrations preferably 8 - 18 ng/ml (10.5 – 23.6 nmol/l)) on top of standard of care is superior in reducing a composite of all-cause mortality and hospitalization for worsening heart failure (whichever occurs first) in patients with advanced systolic chronic heart failure (NYHA class III-IV and EF ≤ 40% or NYHA class II and ≤ 30%) to a greater extent compared to standard care plus placebo.

Protection of trial subjects:

Measurement of digitoxin serum concentration at dose titration six weeks after randomisation (and 12 weeks after randomization, only if dose was increased at six weeks), and of digitoxin serum concentration at 12 months after randomisation.

Background therapy:

guideline-directed medical therapy for patients with chronic heart failure and a left ventricular ejection fraction ≤40% and New York Heart Association [NYHA] functional class ≥III or a left ventricular ejection fraction ≤30% and NYHA functional class II

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 April 2015 |
| 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 | Austria: 33 |
| Country: Number of subjects enrolled | Germany: 1078 |
| Country: Number of subjects enrolled | Serbia: 101 |
| Worldwide total number of subjects | 1212 |
| EEA total number of subjects | 1111 |

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) | 521 |
| From 65 to 84 years | 671 |
| 85 years and over | 20 |

## Subject disposition

### Recruitment

Recruitment details:

Start of recruitment: 04.05.2015
Randomization of last patient: 29.09.2023
Recruitment in Germany, Austria, Serbia

### Pre-assignment

Screening details:

Patients with advanced systolic chronic heart failure NYHA class III-IV and ejection fraction ≤ 40 % or NYHA class II and ejection fraction ≤ 30% who are at least 18 years of age will be screened. They will be recruited from the clinics of the participating centers.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Digitoxin |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Digitoxin AWD 0 07 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One tablet (0,07 mg Digitoxin) per os daily

| | |
|---|---|
| **Arm title** | Placebo |

Arm description: -

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

Dosage and administration details:

Placebo per os daily (0,05 mg or 0,07 mg or 0,1mg)

| **Number of subjects in period 1** | Digitoxin | Placebo |
|---|---|---|
| Started | 613 | 599 |
| Completed | 596 | 591 |
| Not completed | 17 | 8 |
| Lost to follow-up | 17 | 8 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Digitoxin |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Reporting group values | Digitoxin | Placebo | Total |
|---|---|---|---|
| Number of subjects | 613 | 599 | 1212 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 266 | 255 | 521 |
| From 65-84 years | 336 | 335 | 671 |
| 85 years and over | 11 | 9 | 20 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 122 | 125 | 247 |
| Male | 491 | 474 | 965 |

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | Digitoxin |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Primary: Composite endpoint of time to all-cause mortalitiy /heart failure hospitalisation (whichever occurs first) | |
|---|---|
| End point title | Composite endpoint of time to all-cause mortalitiy /heart failure hospitalisation (whichever occurs first) |
| End point description: | |
| End point type | Primary |
| End point timeframe:<br>individual study start to individual event | |

| End point values | Digitoxin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 613 | 599 | | |
| Units: events / 100 patient years | | | | |
| number (not applicable) | 12.8 | 15.7 | | |

### Statistical analyses

| Statistical analysis title | ITT |
|---|---|
| Comparison groups | Digitoxin v Placebo |
| Number of subjects included in analysis | 1212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 0.98 |

| Primary: Time to all-cause death | |
|---|---|
| End point title | Time to all-cause death |
| End point description: | |

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| individual study start to indiviual event | |

| End point values | Digitoxin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 613 | 599 | | |
| Units: events / 100 patient years | | | | |
| number (not applicable) | 7.8 | 8.9 | | |

**Statistical analyses**

| Statistical analysis title | ITT |
|---|---|
| Comparison groups | Digitoxin v Placebo |
| Number of subjects included in analysis | 1212 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.05 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.86 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.07 |

| Primary: Time to first heart failure hospitalisation | |
|---|---|
| End point title | Time to first heart failure hospitalisation |
| End point description: | |

| | |
|---|---|
| End point type | Primary |
| End point timeframe: | |
| individual study start to individual event | |

| End point values | Digitoxin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 613 | 599 | | |
| Units: events / 100 patient years | | | | |
| number (not applicable) | 9.1 | 10.8 | | |

**Statistical analyses**

| Statistical analysis title | ITT |
|---|---|
| Comparison groups | Digitoxin v Placebo |
| Number of subjects included in analysis | 1212 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | < 0.05 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.69 |
| upper limit | 1.05 |

**Secondary: All-cause death and total heart failure hospitalisations**

| End point title | All-cause death and total heart failure hospitalisations |
|---|---|

End point description:

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

End point timeframe:
individual study start to individual event

| End point values | Digitoxin | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 613 | 599 | | |
| Units: events / 100 patient years | | | | |
| number (not applicable) | 25.1 | 26.6 | | |

**Statistical analyses**

| Statistical analysis title | ITT |
|---|---|
| Comparison groups | Digitoxin v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 1212 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | adjusted negative binomial model |
| Parameter estimate | rate ratio |
| Point estimate | 0.85 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.09 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The AE documentation period The documentation period of these events begin upon first administration of the IMP (after baseline visit) and ends at the end of the study.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 27.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Digitoxin |
| Reporting group description: - | |
| Reporting group title | Placebo |

Reporting group description: -

| Serious adverse events | Digitoxin | Placebo | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 613 (4.73%) | 17 / 599 (2.84%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Toxicity to various agents | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gangrene | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulseless electrical activity | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmic storm | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure chronic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiorenal syndrome | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 10 / 613 (1.63%) | 3 / 599 (0.50%) | |
| occurrences causally related to treatment / all | 0 / 11 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Ventricular assist device insertion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Bursitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis clostridial | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Digitoxin | Placebo | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 369 / 613 (60.20%) | 341 / 599 (56.93%) | |
| Vascular disorders | | | |
| Arteriovenous fistula | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Achenbach syndrome | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Aneurysm | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Aortic stenosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Blood pressure fluctuation | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 2 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Extremity necrosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertension | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 3 / 599 (0.50%) | |
| occurrences (all) | 4 | 3 | |
| Hypertensive crisis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Hypotension | | | |
| subjects affected / exposed | 18 / 613 (2.94%) | 10 / 599 (1.67%) | |
| occurrences (all) | 18 | 11 | |
| Iliac artery stenosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ischaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Jugular vein occlusion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Lymphatic fistula | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Peripheral artery stenosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peripheral venous disease | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Scalp haematoma | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Venous occlusion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Bleeding varicose vein | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Surgical and medical procedures | | | |
| Cardiac resynchronisation therapy | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 1 / 599 (0.17%) | |
| occurrences (all) | 3 | 1 | |
| Cardioversion | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 6 / 599 (1.00%) | |
| occurrences (all) | 4 | 8 | |
| Carotid endarterectomy | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cataract operation | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 0 / 599 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Cerebrospinal fluid drainage | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Fistula repair | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Implantable defibrillator insertion | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Implantable defibrillator replacement | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Large intestinal polypectomy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Mitral valve repair | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Salpingo-oophorectomy bilateral | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|---|---|---|---|
| Skin cyst excision | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Skin lesion removal | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Tooth extraction | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 5 | |
| Ventricular assist device insertion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Wrist surgery | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 21 / 613 (3.43%) | 12 / 599 (2.00%) | |
| occurrences (all) | 21 | 12 | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 1 / 599 (0.17%) | |
| occurrences (all) | 5 | 1 | |
| Chest discomfort | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 3 / 599 (0.50%) | |
| occurrences (all) | 6 | 3 | |
| Chest pain | | | |
| subjects affected / exposed | 7 / 613 (1.14%) | 13 / 599 (2.17%) | |
| occurrences (all) | 8 | 14 | |
| Chills | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Condition aggravated | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cyst | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Drug intolerance | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 4 | 2 | |
| Exercise tolerance decreased | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Foreign body reaction | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Generalised oedema | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Illness | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Implant site pain | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Influenza like illness | | | |
| subjects affected / exposed | 16 / 613 (2.61%) | 18 / 599 (3.01%) | |
| occurrences (all) | 16 | 26 | |
| Localised oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Malaise | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 1 / 599 (0.17%) | |
| occurrences (all) | 5 | 1 | |
| Medical device site discomfort | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Medical device site fistula | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Medical device site haemorrhage | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Oedema | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 3 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 16 / 613 (2.61%) | 8 / 599 (1.34%) | |
| occurrences (all) | 18 | 8 | |
| Pain | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 2 / 599 (0.33%) | |
| occurrences (all) | 6 | 2 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 6 / 599 (1.00%) | |
| occurrences (all) | 4 | 6 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 3 / 599 (0.50%) | |
| occurrences (all) | 1 | 3 | |
| Swelling | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thirst | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Immune system disorders | | | |
| Allergy to arthropod sting | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Amyloidosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Rubber sensitivity | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Reproductive system and breast disorders | | | |
| Benign prostatic hyperplasia | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 2 / 599 (0.33%) | |
| occurrences (all) | 5 | 2 | |
| Breast engorgement | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Erectile dysfunction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 2 / 599 (0.33%) | |
| occurrences (all) | 1 | 2 | |
| Gynaecomastia | | | |
| subjects affected / exposed | 8 / 613 (1.31%) | 3 / 599 (0.50%) | |
| occurrences (all) | 8 | 3 | |
| Haematospermia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nipple pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Penile swelling | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peyronie's disease | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Postmenopausal haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Prostatic disorder | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Prostatitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Uterine polyp | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Asthma | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 0 / 599 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Cough | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 8 / 599 (1.34%) | |
| occurrences (all) | 6 | 9 | |
| Diaphragmatic spasm | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Dysphonia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 18 / 613 (2.94%) | 23 / 599 (3.84%) | |
| occurrences (all) | 23 | 28 | |
| Dyspnoea at rest | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 7 / 613 (1.14%) | 4 / 599 (0.67%) | |
| occurrences (all) | 9 | 4 | |
| Dyspnoea paroxysmal nocturnal | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 7 / 599 (1.17%) | |
| occurrences (all) | 8 | 7 | |
| Nasal septum deviation | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nocturnal dyspnoea | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Obstructive airways disorder | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Obstructive sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Oropharyngeal pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Orthopnoea | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 5 / 599 (0.83%) | |
| occurrences (all) | 2 | 5 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 2 | |
| Productive cough | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 1 / 599 (0.17%) | |
| occurrences (all) | 3 | 1 | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Pulmonary fibrosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Pulmonary oedema | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 0 / 599 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rhonchi | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 2 / 599 (0.33%) | |
| occurrences (all) | 5 | 2 | |
| Tracheal pain | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vocal cord erythema | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Vocal cord inflammation | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypersensitivity pneumonitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal turbinate hypertrophy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychiatric disorders | | | |

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|---|---|---|---|
| Nervousness | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aggression | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Anxiety | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Apathy | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Depression | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 3 / 599 (0.50%) | |
| occurrences (all) | 2 | 3 | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Hallucination | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Initial insomnia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 3 / 599 (0.50%) | |
| occurrences (all) | 0 | 3 | |

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|---|---|---|---|
| Intensive care unit delirium | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Middle insomnia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 3 / 599 (0.50%) | |
| occurrences (all) | 1 | 4 | |
| Mood swings | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nightmare | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Panic attack | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Restlessness | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 3 / 599 (0.50%) | |
| occurrences (all) | 4 | 3 | |
| Sleep disorder | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 3 / 599 (0.50%) | |
| occurrences (all) | 6 | 3 | |
| Product issues | | | |
| Device pacing issue | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Device malfunction | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 2 | |
| Investigations | | | |
| Arthroscopy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Catheterisation cardiac | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Blood bilirubin increased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Blood creatine phosphokinase increased | | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 2 | 0 | | |
| Blood creatinine increased | | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 3 | 0 | | |
| Blood glucose fluctuation | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Blood glucose increased | | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 2 | 0 | | |
| Blood potassium decreased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Blood potassium increased | | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 4 | 1 | | |
| Blood pressure abnormal | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | | |
| occurrences (all) | 0 | 2 | | |
| Blood pressure increased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Blood thyroid stimulating hormone decreased | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Blood triglycerides increased | | | | |

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|---|---|---|---|
| subjects affected / exposed | 5 / 613 (0.82%) | 0 / 599 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Blood uric acid increased | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 2 / 599 (0.33%) | |
| occurrences (all) | 1 | 2 | |
| Blood urine | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood urine present | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Cardiac murmur | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Cardioactive drug level above therapeutic | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Cardioactive drug level increased | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Biopsy heart | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 8 | |
| Glomerular filtration rate decreased | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Glomerular filtration rate abnormal | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 1 / 599 (0.17%) | |
| occurrences (all) | 4 | 1 | |
| Heart rate decreased | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |

| | | | | |
|---|---|---|---|---|
| Heart rate increased | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | | |
| occurrences (all) | 0 | 2 | | |
| Hepatic enzyme increased | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Inflammatory marker increased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| International normalised ratio abnormal | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| International normalised ratio increased | | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 2 | 0 | | |
| Intraocular pressure increased | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Liver function test abnormal | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 1 | 1 | | |
| Liver function test increased | | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 4 | 1 | | |
| N-terminal prohormone brain natriuretic peptide increased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 2 / 599 (0.33%) | | |
| occurrences (all) | 1 | 2 | | |
| Renal function test abnormal | | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 3 | 0 | | |
| Coronavirus test positive | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Device function test | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 613 (0.33%) | 2 / 599 (0.33%) | |
| occurrences (all) | 4 | 2 | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Electrocardiogram PR prolongation | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Electrocardiogram QRS complex abnormal | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 3 / 599 (0.50%) | |
| occurrences (all) | 0 | 3 | |
| Electrocardiogram ST segment depression | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Electrocardiogram change | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 0 / 599 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Glycosylated haemoglobin increased | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 0 / 599 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Sensory level abnormal | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 1 | 1 | | |
| Transaminases increased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Transferrin saturation decreased | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Transplant evaluation | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Troponin T increased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 1 | 1 | | |
| Troponin increased | | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 2 | 1 | | |
| Vascular resistance pulmonary increased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Venous pressure jugular | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Weight decreased | | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 3 / 599 (0.50%) | | |
| occurrences (all) | 7 | 3 | | |
| Weight increased | | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | | |
| occurrences (all) | 3 | 2 | | |
| White blood cell count increased | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Serum ferritin increased | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |

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|---|---|---|---|
| Injury, poisoning and procedural complications | | | |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Anaemia postoperative | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Animal bite | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Arthropod bite | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Contusion | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 4 / 599 (0.67%) | |
| occurrences (all) | 4 | 4 | |
| Coronary artery restenosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Craniofacial fracture | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Electric injury | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 3 / 599 (0.50%) | |
| occurrences (all) | 0 | 3 | |
| Epicondylitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Fall | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 613 (0.65%) | 6 / 599 (1.00%) | |
| occurrences (all) | 5 | 7 | |
| Femur fracture | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 2 | |
| Fibula fracture | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Foot fracture | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Fracture | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Immunisation reaction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 2 | |
| Joint injury | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Limb crushing injury | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Limb injury | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Lip injury | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Lumbar vertebral fracture | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Medication error | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Meniscus injury | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Muscle strain | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasal injury | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Overdose | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 1 / 599 (0.17%) | |
| occurrences (all) | 3 | 1 | |
| Poisoning | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Post procedural complication | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Psychosis postoperative | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Radial nerve injury | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Clavicle fracture | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Skin laceration | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tendon injury | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tendon rupture | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tooth fracture | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Traumatic haematoma | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Traumatic intracranial haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Upper limb fracture | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vascular graft stenosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Wound | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 3 / 599 (0.50%) | |
| occurrences (all) | 3 | 3 | |
| Wrist fracture | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Spinal fracture | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Arteriosclerosis coronary artery | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |

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|---|---|---|---|
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Angina pectoris | | | |
| subjects affected / exposed | 12 / 613 (1.96%) | 9 / 599 (1.50%) | |
| occurrences (all) | 14 | 10 | |
| Angina unstable | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Anophthalmos | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Aortic valve stenosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 2 / 599 (0.33%) | |
| occurrences (all) | 7 | 3 | |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 33 / 613 (5.38%) | 31 / 599 (5.18%) | |
| occurrences (all) | 39 | 34 | |
| Congenital, familial and genetic disorders | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Atrial tachycardia | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 5 / 599 (0.83%) | |
| occurrences (all) | 3 | 5 | |
| Atrial thrombosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Atrioventricular block | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 5 / 599 (0.83%) | |
| occurrences (all) | 3 | 5 | |
| Atrioventricular block first degree | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 5 / 599 (0.83%) | |
| occurrences (all) | 3 | 5 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bradyarrhythmia | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 0 / 599 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 10 / 613 (1.63%) | 3 / 599 (0.50%) | |
| occurrences (all) | 10 | 3 | |
| Bundle branch block left | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 2 / 599 (0.33%) | |
| occurrences (all) | 4 | 2 | |
| Bundle branch block right | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 4 / 599 (0.67%) | |
| occurrences (all) | 0 | 4 | |
| Cardiac aneurysm | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac discomfort | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 29 / 613 (4.73%) | 26 / 599 (4.34%) | |
| occurrences (all) | 43 | 36 | |
| Cardiac failure chronic | | | |

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| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 2 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac fibrillation | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Cardiac tamponade | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cardiac ventricular thrombosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cardiorenal syndrome | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Cardiovascular disorder | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Atrial flutter | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 4 / 599 (0.67%) | |
| occurrences (all) | 2 | 4 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 2 / 599 (0.33%) | |
| occurrences (all) | 1 | 2 | |
| Palpitations | | | |
| subjects affected / exposed | 9 / 613 (1.47%) | 2 / 599 (0.33%) | |
| occurrences (all) | 9 | 2 | |
| Pericarditis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pulseless electrical activity | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 3 / 599 (0.50%) | |
| occurrences (all) | 1 | 3 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 5 / 599 (0.83%) | |
| occurrences (all) | 4 | 5 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 2 / 599 (0.33%) | |
| occurrences (all) | 5 | 2 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 3 / 599 (0.50%) | |
| occurrences (all) | 0 | 3 | |
| Tachycardia | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 7 / 599 (1.17%) | |
| occurrences (all) | 4 | 8 | |
| Tricuspid valve incompetence | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 9 / 599 (1.50%) | |
| occurrences (all) | 6 | 9 | |
| Ventricular fibrillation | | | |
| subjects affected / exposed | 13 / 613 (2.12%) | 5 / 599 (0.83%) | |
| occurrences (all) | 16 | 8 | |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 36 / 613 (5.87%) | 38 / 599 (6.34%) | |
| occurrences (all) | 58 | 82 | |
| Coronary artery disease | | | |

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|---|---|---|---|
| subjects affected / exposed | 5 / 613 (0.82%) | 1 / 599 (0.17%) | |
| occurrences (all) | 5 | 1 | |
| Coronary artery stenosis | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 1 / 599 (0.17%) | |
| occurrences (all) | 3 | 1 | |
| Extrasystoles | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nervous system disorders | | | |
| Ageusia | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 2 | |
| Aphasia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |

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|---|---|---|---|---|
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Chronic inflammatory demyelinating polyradiculoneuropathy | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Cognitive disorder | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Cold dysaesthesia | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Diabetic neuropathy | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 1 | 1 | | |
| Dizziness | | | | |
| subjects affected / exposed | 47 / 613 (7.67%) | 39 / 599 (6.51%) | | |
| occurrences (all) | 52 | 43 | | |
| Dizziness exertional | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Dizziness postural | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 3 / 599 (0.50%) | | |
| occurrences (all) | 1 | 3 | | |
| Epilepsy | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 4 | 1 | | |
| Headache | | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 12 / 599 (2.00%) | | |
| occurrences (all) | 5 | 13 | | |
| Hypersomnia | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Hypoaesthesia | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Hypoglycaemic unconsciousness | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Lumbosacral radiculopathy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Memory impairment | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Migraine | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Migraine with aura | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Neuromyopathy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nystagmus | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 5 / 599 (0.83%) | |
| occurrences (all) | 7 | 5 | |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 3 / 599 (0.50%) | |
| occurrences (all) | 1 | 3 | |
| Parkinsonism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 4 | 2 | |
| Poor quality sleep | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sciatica | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Seizure | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Sensory disturbance | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Somnolence | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Syncope | | | |
| subjects affected / exposed | 22 / 613 (3.59%) | 13 / 599 (2.17%) | |
| occurrences (all) | 23 | 15 | |
| Taste disorder | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tongue biting | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Tremor | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 2 | |
| Vertebral artery occlusion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Visual field defect | | | |

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| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Presyncope | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 3 / 599 (0.50%) | |
| occurrences (all) | 2 | 3 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 8 / 613 (1.31%) | 3 / 599 (0.50%) | |
| occurrences (all) | 9 | 3 | |
| Coagulopathy | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Haemorrhagic diathesis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 3 / 599 (0.50%) | |
| occurrences (all) | 5 | 3 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Macrocytosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Microcytic anaemia | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Polycythaemia | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |

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| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 2 | |
| Ear and labyrinth disorders | | | |
| Ear discomfort | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ear pain | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypoacusis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Middle ear effusion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Middle ear inflammation | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sudden hearing loss | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tinnitus | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 1 / 599 (0.17%) | |
| occurrences (all) | 3 | 1 | |
| Vertigo | | | |
| subjects affected / exposed | 12 / 613 (1.96%) | 8 / 599 (1.34%) | |
| occurrences (all) | 15 | 10 | |
| Vertigo positional | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eye disorders | | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Amaurosis fugax | | | |

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| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 2 | |
| Blepharitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cataract | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 4 / 599 (0.67%) | |
| occurrences (all) | 6 | 4 | |
| Chromatopsia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Corneal deposits | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Endocrine ophthalmopathy | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Eye haematoma | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Eye haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Optic atrophy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Photophobia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Pseudophakia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Retinopathy | | | |

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| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Visual field defect | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Visual impairment | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 10 / 599 (1.67%) | |
| occurrences (all) | 3 | 10 | |
| Vitreous detachment | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myopia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 7 / 599 (1.17%) | |
| occurrences (all) | 2 | 7 | |
| Abdominal distension | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 3 / 599 (0.50%) | |
| occurrences (all) | 2 | 3 | |
| Abdominal hernia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 5 / 599 (0.83%) | |
| occurrences (all) | 1 | 5 | |

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| Abdominal pain lower | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 5 / 599 (0.83%) | |
| occurrences (all) | 5 | 7 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Nausea | | | |
| subjects affected / exposed | 29 / 613 (4.73%) | 22 / 599 (3.67%) | |
| occurrences (all) | 33 | 23 | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Large intestine polyp | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Intestinal polyp | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Inguinal hernia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hiatus hernia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |

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|---|---|---|---|
| Haemorrhagic erosive gastritis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Haematochezia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 3 / 599 (0.50%) | |
| occurrences (all) | 1 | 4 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 2 | |
| Gastrointestinal inflammation | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 1 / 599 (0.17%) | |
| occurrences (all) | 3 | 1 | |
| Gastritis haemorrhagic | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastritis | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 5 / 599 (0.83%) | |
| occurrences (all) | 3 | 5 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Enterocolitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Dysphagia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 6 / 599 (1.00%) | |
| occurrences (all) | 3 | 6 | |
| Duodenitis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |

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|---|---|---|---|
| Diverticulum intestinal | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 37 / 613 (6.04%) | 18 / 599 (3.01%) | |
| occurrences (all) | 44 | 18 | |
| Constipation | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 2 / 599 (0.33%) | |
| occurrences (all) | 6 | 2 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chronic gastrointestinal bleeding | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chronic gastritis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 3 / 599 (0.50%) | |
| occurrences (all) | 2 | 3 | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Anal incontinence | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 8 / 613 (1.31%) | 5 / 599 (0.83%) | |
| occurrences (all) | 11 | 5 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Toothache | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |

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|---|---|---|---|
| Swollen tongue | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Salivary gland calculus | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Retching | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatobiliary disorders | | | |
| Hepatic lesion | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bile duct stone | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Congestive hepatopathy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Hepatic steatosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hepatomegaly | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Actinic keratosis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 4 / 599 (0.67%) | |
| occurrences (all) | 2 | 4 | |
| Blister | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermal cyst | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Eczema | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |

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|---|---|---|---|
| Erythema | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 1 / 599 (0.17%) | |
| occurrences (all) | 3 | 1 | |
| Hirsutism | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 7 / 599 (1.17%) | |
| occurrences (all) | 6 | 8 | |
| Ingrowing nail | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Nail psoriasis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Night sweats | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Onychoclasis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pigmentation disorder | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 7 / 613 (1.14%) | 10 / 599 (1.67%) | |
| occurrences (all) | 7 | 10 | |
| Psoriasis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pyoderma gangrenosum | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 5 / 599 (0.83%) | |
| occurrences (all) | 6 | 5 | |

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|---|---|---|---|
| Skin disorder | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Skin erosion | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin induration | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin irritation | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin ulcer | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 0 / 599 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Stasis dermatitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Swelling face | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Urticaria | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Renal and urinary disorders | | | |
| Ureteric stenosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urethral stenosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal impairment | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 5 / 613 (0.82%) | 2 / 599 (0.33%) | | |
| occurrences (all) | 5 | 2 | | |
| Renal failure | | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 2 / 599 (0.33%) | | |
| occurrences (all) | 6 | 2 | | |
| Renal cyst | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 1 | 1 | | |
| Prerenal failure | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Pollakiuria | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 1 | 1 | | |
| Oliguria | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Nocturia | | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 2 | 0 | | |
| Nephrolithiasis | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Leukocyturia | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Incontinence | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Haematuria | | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 3 / 599 (0.50%) | | |
| occurrences (all) | 2 | 3 | | |
| Dysuria | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Cystitis noninfective | | | | |

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|---|---|---|---|
| subjects affected / exposed | 4 / 613 (0.65%) | 1 / 599 (0.17%) | |
| occurrences (all) | 4 | 1 | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 10 / 613 (1.63%) | 12 / 599 (2.00%) | |
| occurrences (all) | 15 | 12 | |
| Urethral obstruction | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Urethral haemorrhage | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Renal mass | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract inflammation | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Urinary hesitation | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 2 | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |

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|---|---|---|---|
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Hypothyroidism | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 1 / 599 (0.17%) | |
| occurrences (all) | 4 | 1 | |
| Toxic nodular goitre | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Adenocarcinoma of colon | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 9 / 599 (1.50%) | |
| occurrences (all) | 5 | 11 | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Arthropathy | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Back pain | | | |
| subjects affected / exposed | 11 / 613 (1.79%) | 6 / 599 (1.00%) | |
| occurrences (all) | 11 | 6 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 2 | |
| Bowen's disease | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Bursa disorder | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Bursitis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Coccydynia | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Colorectal adenoma | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Diffuse large B-cell lymphoma recurrent | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Exostosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gouty arthritis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 3 / 599 (0.50%) | |
| occurrences (all) | 2 | 3 | |
| Haemarthrosis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Joint effusion | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint impingement | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Joint range of motion decreased | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |

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|---|---|---|---|
| Joint swelling | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 3 | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Meniscal degeneration | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metastases to bone | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Muscle discomfort | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 9 / 613 (1.47%) | 4 / 599 (0.67%) | |
| occurrences (all) | 10 | 4 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Musculoskeletal discomfort | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 3 / 599 (0.50%) | |
| occurrences (all) | 5 | 3 | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 4 / 599 (0.67%) | |
| occurrences (all) | 3 | 5 | |
| Myeloproliferative neoplasm | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | | |
|---|---|---|---|---|
| Myopathy | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | | |
| subjects affected / exposed | 9 / 613 (1.47%) | 9 / 599 (1.50%) | | |
| occurrences (all) | 10 | 14 | | |
| Oesophageal carcinoma | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Osteoarthritis | | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 7 / 599 (1.17%) | | |
| occurrences (all) | 5 | 12 | | |
| Osteochondrosis | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 1 | 1 | | |
| Osteolysis | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 1 | 1 | | |
| Osteopenia | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 2 | 0 | | |
| Pain in extremity | | | | |
| subjects affected / exposed | 10 / 613 (1.63%) | 4 / 599 (0.67%) | | |
| occurrences (all) | 11 | 4 | | |
| Pain in jaw | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Plantar fasciitis | | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | | |
| occurrences (all) | 1 | 0 | | |
| Polyarthritis | | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | | |
| occurrences (all) | 0 | 1 | | |
| Polymyalgia rheumatica | | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 3 / 599 (0.50%) | |
| occurrences (all) | 1 | 3 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Rheumatoid arthritis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Rotator cuff syndrome | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Skin papilloma | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Spinal pain | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 3 / 599 (0.50%) | |
| occurrences (all) | 2 | 3 | |
| Spondylitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 2 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tendon pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Thymoma malignant recurrent | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Tongue neoplasm | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Weight bearing difficulty | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Neck mass | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infections and infestations | | | |
| Arthritis infective | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Abscess of external ear | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Abscess oral | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Acarodermatitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 25 / 613 (4.08%) | 21 / 599 (3.51%) | |
| occurrences (all) | 31 | 25 | |
| Bacterial disease carrier | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 2 / 599 (0.33%) | |
| occurrences (all) | 1 | 2 | |

| | | | |
|---|---|---|---|
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Bronchitis | | | |
| subjects affected / exposed | 11 / 613 (1.79%) | 15 / 599 (2.50%) | |
| occurrences (all) | 13 | 15 | |
| COVID-19 | | | |
| subjects affected / exposed | 31 / 613 (5.06%) | 28 / 599 (4.67%) | |
| occurrences (all) | 32 | 29 | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Coronavirus infection | | | |
| subjects affected / exposed | 7 / 613 (1.14%) | 13 / 599 (2.17%) | |
| occurrences (all) | 7 | 14 | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Diabetic foot infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Enterococcal infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Enterocolitis bacterial | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Erysipelas | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 2 / 599 (0.33%) | |
| occurrences (all) | 4 | 2 | |
| Febrile infection | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Furuncle | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |

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|---|---|---|---|
| Gangrene | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 7 / 613 (1.14%) | 9 / 599 (1.50%) | |
| occurrences (all) | 7 | 10 | |
| Gastroenteritis clostridial | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Gingivitis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Groin abscess | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 2 / 599 (0.33%) | |
| occurrences (all) | 6 | 2 | |
| Hordeolum | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Impetigo | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Implant site infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Infection | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 2 | |
| Influenza | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 5 / 599 (0.83%) | |
| occurrences (all) | 3 | 5 | |

| | | | |
|---|---|---|---|
| Klebsiella infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Mastitis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral fungal infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral herpes | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Orchitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Otitis media | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Penile infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|---|---|---|
| Periodontitis | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 17 / 599 (2.84%) | |
| occurrences (all) | 7 | 18 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Post-acute COVID-19 syndrome | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Pulpitis dental | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 12 / 613 (1.96%) | 9 / 599 (1.50%) | |
| occurrences (all) | 13 | 9 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Severe acute respiratory syndrome | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sialoadenitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|---|---|---|
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 2 / 599 (0.33%) | |
| occurrences (all) | 1 | 2 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Superinfection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Tinea pedis | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 3 / 599 (0.50%) | |
| occurrences (all) | 5 | 3 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 9 / 613 (1.47%) | 9 / 599 (1.50%) | |
| occurrences (all) | 9 | 13 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Wound infection | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Metabolism and nutrition disorders | | | |
| Abnormal loss of weight | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Cachexia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 2 / 599 (0.33%) | |
| occurrences (all) | 2 | 2 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 9 / 613 (1.47%) | 8 / 599 (1.34%) | |
| occurrences (all) | 9 | 8 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 7 / 613 (1.14%) | 5 / 599 (0.83%) | |
| occurrences (all) | 7 | 5 | |
| Folate deficiency | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Food aversion | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Food craving | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 2 / 599 (0.33%) | |
| occurrences (all) | 0 | 2 | |
| Gout | | | |
| subjects affected / exposed | 19 / 613 (3.10%) | 10 / 599 (1.67%) | |
| occurrences (all) | 29 | 13 | |
| Hypercholesterolaemia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 3 / 613 (0.49%) | 2 / 599 (0.33%) | |
| occurrences (all) | 3 | 2 | |
| Hyperkalaemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 22 / 613 (3.59%) | 25 / 599 (4.17%) | |
| occurrences (all) | 24 | 26 | |
| Hyperlipidaemia | | | |
| subjects affected / exposed | 0 / 613 (0.00%) | 1 / 599 (0.17%) | |
| occurrences (all) | 0 | 1 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertriglyceridaemia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 4 / 613 (0.65%) | 1 / 599 (0.17%) | |
| occurrences (all) | 4 | 1 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 9 / 613 (1.47%) | 12 / 599 (2.00%) | |
| occurrences (all) | 10 | 12 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 1 / 599 (0.17%) | |
| occurrences (all) | 2 | 1 | |
| Iron deficiency | | | |
| subjects affected / exposed | 5 / 613 (0.82%) | 0 / 599 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 1 / 599 (0.17%) | |
| occurrences (all) | 1 | 1 | |
| Type 1 diabetes mellitus | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 613 (0.16%) | 0 / 599 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 6 / 613 (0.98%) | 4 / 599 (0.67%) | |
| occurrences (all) | 6 | 4 | |
| Vitamin B12 deficiency | | | |
| subjects affected / exposed | 2 / 613 (0.33%) | 0 / 599 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 613 (0.16%) | 2 / 599 (0.33%) | |
| occurrences (all) | 1 | 2 | |
| Decreased appetite | | | |
| subjects affected / exposed | 8 / 613 (1.31%) | 3 / 599 (0.50%) | |
| occurrences (all) | 8 | 3 | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 23 February 2016 | SA No. 1: Protocol Vs. 2.0 dated 26.01.2016<br>Change Inclusion Criteria 4 (Patients with chronic heart failure NYHA class III-IV and aventricular ejection fraction of EF ≤ 40%* or patients with heart failure NYHA class II and EF ≤ 30 %* (* % (determined at screening by echocardiography or cardiac magnetic resonance tomography or within 8 weeks prior to study inclusion by left-ventricular angiography, echocardiography, radionuclide ventriculography, cardiac magnetic resonance tomography AND an evidence based heart failure therapy at least for six months upon discretion of the treating physician)<br>Change Exclusion Criteria 1 (Recent (< 2 months ago): myocardial infarction, coronary revascularization, acute coronary syndrome, stroke or cerebral ischemia and start of heart failure device therapy potentially improving left ventricular ejection fraction or heart failure symptoms (e.g. cardiac resynchronization therapy (CRT), cardiac contractility modulation (CCM), baroreflex-activation therapy (BAT))<br>Change Exclusion Criteria 2 Scheduled surgery or catheter intervention for valvular heart disease or scheduled coronary revascularization)<br>Change Exclusion Criteria 4 (Complex congenital heart disease; this does not include: mild-moderate valve disease, uncomplicated shunts (isolated patent foramen ovale, small atrial 3 or ventricular septum defects without associated lesions), repaired secundum or sinus venosus atrial septal defects and ventricular septal defects without residua, previously ligated or occluded ductus arteriosus)<br>Change Exclusion Criteria 5 (High-urgency listing for heart transplantation or scheduled therapy with left ventricular assist device (LVAD))<br>Change of Exclusion Criteria 14 (Thoracic aortic aneurysm (defined as diameter ≥ 45 mm))<br>Change of Exclusion Criteria 18 and Exclusion Criteria 26<br>Clarification of the possible administration of amiodarone<br>Addition of an additional digitoxin determination after 1 year |
| 08 March 2017 | SA No. 2: Protocol Vs. 3.0 dated 06.02.2017<br>Approval Germany 08.03.2017 (BfArM) and 16.03.2017 (IEC MHH)<br><br>- Change/specification of the exclusion criterion 1 (Recent (< 2 months ago): myocardial infarction, coronary revascularization, surgery or catheter intervention for valvular heart disease, acute coronary syndrome, stroke or cerebral ischemia and start of heart failure device therapy potentially improving left ventricular ejection fraction or heart failure symptoms (e.g. cardiac resynchronization therapy (CRT), cardiac contractility modulation (CCM), baroreflexactivation therapy (BAT)))<br>- Change/specification of the exclusion criterion 6 (Heart rate < 60 b.p.m. (except if ffunctional CRT in place)).<br>- Change/specification of the exclusion criterion 20 (Presence of both treatment with cardiac glycosides and atrial fibrillation).<br>- Addition of the exclusion criterion 27 (Life expectancy < 12 month (e.g. due to active cancer)). |

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| 09 March 2018 | SA No. 3: Protocol Vs. 4.1 dated 06.02.2018<br>Clarification of inclusion criteria 2 (Male or female patients age ≥ 18 years at day of iinclusion)<br>Change/specification inclusion criterion 5 (Women without childbearing potential defined as one or more of following: * Women at least 6 weeks after surgical sterilization by bilateral tubal ligation or bilateral oophorectomy with or without hysterectomy, * Women ≥ 50 years of age at the day of inclusion who have been postmenopausal since at least 1 year, * Women < 50 years and in postmenopausal state ≥ 1 year with serum FSH > 40 IU/l OR Women of childbearing potential who have a negative hCG pregnancy test and agree to meet one of the following criteria from the time of screening/baseline, during the study and for a period of 40 days following the last administration of study medication: * Correct use of reliable contraception methods. This includes hormonal contraceptive or an intrauterine device or a barrier method of contraception such as condom or occlusive cap with spermicide, * True abstinence, * Sexual relationship only with female partners and/or sterile male partners OR Men<br>Clarification of exclusion criteria 1 (Recent: myocardial infarction, coronary revascularization, surgery or catheter intervention for valvular heart disease, acute coronary syndrome, stroke or cerebral ischema ...<br>Clarification of exclusion criteria 4<br>Recruitment period extension (ca72 months in total)<br>Clarification of time frame (event-driven)<br>Addition of 2 substudies (effect of digitoxin on arrhythmia burden / endothelial function)<br>Dose adjustment for digitoxin serum concentrations (25 ng/ml (33 nmol/l)<br>Introduction of telephone FU visits for participants who are no longer taking IMP<br>Change in procedure for endpoint adjudication<br>No determination of digitoxin serum conc. if study medication is not taken<br>Introduction of the option to query health insurance companies<br>Change AE documentation<br>Data management and monitoring |
| 02 May 2019 | SA No. 4: Protocol Vs. 5.0 dated 06.02.2019<br>Approval Germany 02.05.2019 (BfArM) and 22.05.2019 (IEC MHH)<br>Approval Austria: 14.05.2019 (BASG) and 29.05.2019 (IEC Wien)<br>Approval Serbia: 21.10.2020 (Serbian Agency for Medicines and Medical Devices) and 08.07.2019 (Ethical Board of CHC "Bežanijska kosa", Belgrade)<br><br>- Addition of two substudies on the effect of digitoxin on exercise capacity and echocardiographic remodeling<br>- Specification/supplement to the exclusion criterion 2 (Scheduled surgery or catheter intervention for valvular heart disease, scheduled coronary revascularization, scheduled heart ffailure device therapy potentially improving left ventricular ejection fraction or heart failure symptoms (e.g. cardiac resynchronization therapy (CRT), cardiac contractility modulation (CCM), baroreflex-activation therapy (BAT)))<br>- Additions to the procedure for adjusting the dose of the IMP<br>- Change of sponsor contact person<br>- Change in the legal form of the CRO |
| 14 August 2020 | SA No. 5: Protocol Vs. 6.0 dated 16.07.2020<br>Approval Germany 14.08.2020 (BfArM) and 05.10.2020 (IEC MHH)<br>Approval Austria: 23.12.2020 (BASG) and 20.11.2020 (IEC Wien)<br>Approval Serbia: 08.04.2022 (Serbian Agency for Medicines and Medical Devices, including IEC)<br><br>Intermittend measures due to Covid-19/Corona pandemic for recruitment, IMP allocation, drug accountability, trial visits, collection of blood samples, monitoring |

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|---|---|
| 20 April 2022 | SA No. 6: Protocol Vs. 7.0 dated 14.12.2021<br>Approval Germany 20.04.2022 (BfArM) and 19.05.2022 (IEC MHH)<br>Approval Austria: 31.05.2022 (BASG) and 17.05.2022 (IEC Wien)<br>Approval Serbia: 24.08.2023 (Serbian Agency for Medicines and Medical Devices, including IEC)<br><br>- Adjustment of recruitment and study duration<br>- Adjustment to the updated guideline (addition of Sodium-Glucose-Transporter-2-Inhibitor)<br>- Addition of subgroup analysis for regions ((EU versus Serbia), supplement quadruple therapy in statistical analysis<br>- Clarification: Hospital stay overnight = date change<br>- Removal of SF-12 as an appendix to the protocol due to possible copyright infringement upon publication of the protocol |
| 05 September 2023 | SA No. 7: Protocol Vs. 8.0 dated 20.07.2023<br>Approval Germany 05.09.2023 (BfArM) und 06.09.2023 (IEC MHH)<br>Approval Austria: 14.09.2023 (BASG) und 10.10.2023 (IEC Wien)<br>Approval Serbia: 14.02.2025 (Serbian Agency for Medicines and Medical Devices, including IEC)<br>• Adjustment of recruitment period and study duration<br>• Non-implementation of interim evaluation<br>• Change in key secondary endpoints (and the resulting change in the evaluation method)<br>• Change to the Reference Safety Information (the existing Digimerck® product information will no longer be updated) |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported

## Online references

http://www.ncbi.nlm.nih.gov/pubmed/40389288

http://www.ncbi.nlm.nih.gov/pubmed/37087503

http://www.ncbi.nlm.nih.gov/pubmed/39838553

http://www.ncbi.nlm.nih.gov/pubmed/40879434

http://www.ncbi.nlm.nih.gov/pubmed/30892806