



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
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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 \leq 40% or NYHA class II and \leq 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 \leq 40% and New York Heart Association [NYHA] functional class \geq III or a left ventricular ejection fraction \leq 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 $\leq 40\%$ or NYHA class II and ejection fraction $\leq 30\%$ 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
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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			
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			
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 mortality /heart failure hospitalisation (whichever occurs first)

End point title	Composite endpoint of time to all-cause mortality /heart failure hospitalisation (whichever occurs first)
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)	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
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End point description:

End point type	Primary
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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)	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
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End point description:

End point type	Primary
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	27.1
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Reporting groups

Reporting group title	Digitoxin
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Reporting group description: -

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

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

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		

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			

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

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

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		

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

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		

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		

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	

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

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		

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		

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		

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	

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		

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	

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

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		

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

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

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

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

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			

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

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
Onychoclasia		
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

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			

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		

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	

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			

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

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		

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

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	<p>SA No. 1: Protocol Vs. 2.0 dated 26.01.2016</p> <p>Change Inclusion Criteria 4 (Patients with chronic heart failure NYHA class III-IV and a ventricular ejection fraction of $EF \leq 40\%$* or patients with heart failure NYHA class II and $EF \leq 30\%$* (* % (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)</p> <p>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))</p> <p>Change Exclusion Criteria 2 Scheduled surgery or catheter intervention for valvular heart disease or scheduled coronary revascularization)</p> <p>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)</p> <p>Change Exclusion Criteria 5 (High-urgency listing for heart transplantation or scheduled therapy with left ventricular assist device (LVAD))</p> <p>Change of Exclusion Criteria 14 (Thoracic aortic aneurysm (defined as diameter ≥ 45 mm))</p> <p>Change of Exclusion Criteria 18 and Exclusion Criteria 26</p> <p>Clarification of the possible administration of amiodarone</p> <p>Addition of an additional digitoxin determination after 1 year</p>
08 March 2017	<p>SA No. 2: Protocol Vs. 3.0 dated 06.02.2017</p> <p>Approval Germany 08.03.2017 (BfArM) and 16.03.2017 (IEC MHH)</p> <ul style="list-style-type: none">- 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)))- Change/specification of the exclusion criterion 6 (Heart rate < 60 b.p.m. (except if functional CRT in place)).- Change/specification of the exclusion criterion 20 (Presence of both treatment with cardiac glycosides and atrial fibrillation).- Addition of the exclusion criterion 27 (Life expectancy < 12 month (e.g. due to active cancer)).

09 March 2018	<p>SA No. 3: Protocol Vs. 4.1 dated 06.02.2018</p> <p>Clarification of inclusion criteria 2 (Male or female patients age ≥ 18 years at day of inclusion)</p> <p>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</p> <p>Clarification of exclusion criteria 1 (Recent: myocardial infarction, coronary revascularization, surgery or catheter intervention for valvular heart disease, acute coronary syndrome, stroke or cerebral ischemia ...</p> <p>Clarification of exclusion criteria 4</p> <p>Recruitment period extension (ca72 months in total)</p> <p>Clarification of time frame (event-driven)</p> <p>Addition of 2 substudies (effect of digitoxin on arrhythmia burden / endothelial function)</p> <p>Dose adjustment for digitoxin serum concentrations (25 ng/ml (33 nmol/l)</p> <p>Introduction of telephone FU visits for participants who are no longer taking IMP</p> <p>Change in procedure for endpoint adjudication</p> <p>No determination of digitoxin serum conc. if study medication is not taken</p> <p>Introduction of the option to query health insurance companies</p> <p>Change AE documentation</p> <p>Data management and monitoring</p>
02 May 2019	<p>SA No. 4: Protocol Vs. 5.0 dated 06.02.2019</p> <p>Approval Germany 02.05.2019 (BfArM) and 22.05.2019 (IEC MHH)</p> <p>Approval Austria: 14.05.2019 (BASG) and 29.05.2019 (IEC Wien)</p> <p>Approval Serbia: 21.10.2020 (Serbian Agency for Medicines and Medical Devices) and 08.07.2019 (Ethical Board of CHC "Bežanijska kosa", Belgrade)</p> <ul style="list-style-type: none"> - Addition of two substudies on the effect of digitoxin on exercise capacity and echocardiographic remodeling - Specification/supplement to the exclusion criterion 2 (Scheduled surgery or catheter intervention for valvular heart disease, scheduled coronary revascularization, scheduled 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))) - Additions to the procedure for adjusting the dose of the IMP - Change of sponsor contact person - Change in the legal form of the CRO
14 August 2020	<p>SA No. 5: Protocol Vs. 6.0 dated 16.07.2020</p> <p>Approval Germany 14.08.2020 (BfArM) and 05.10.2020 (IEC MHH)</p> <p>Approval Austria: 23.12.2020 (BASG) and 20.11.2020 (IEC Wien)</p> <p>Approval Serbia: 08.04.2022 (Serbian Agency for Medicines and Medical Devices, including IEC)</p> <p>Intermittend measures due to Covid-19/Corona pandemic for recruitment, IMP allocation, drug accountability, trial visits, collection of blood samples, monitoring</p>

20 April 2022	<p>SA No. 6: Protocol Vs. 7.0 dated 14.12.2021 Approval Germany 20.04.2022 (BfArM) and 19.05.2022 (IEC MHH) Approval Austria: 31.05.2022 (BASG) and 17.05.2022 (IEC Wien) Approval Serbia: 24.08.2023 (Serbian Agency for Medicines and Medical Devices, including IEC)</p> <ul style="list-style-type: none"> - Adjustment of recruitment and study duration - Adjustment to the updated guideline (addition of Sodium-Glucose-Transporter-2-Inhibitor) - Addition of subgroup analysis for regions ((EU versus Serbia), supplement quadruple therapy in statistical analysis - Clarification: Hospital stay overnight = date change - Removal of SF-12 as an appendix to the protocol due to possible copyright infringement upon publication of the protocol
05 September 2023	<p>SA No. 7: Protocol Vs. 8.0 dated 20.07.2023 Approval Germany 05.09.2023 (BfArM) und 06.09.2023 (IEC MHH) Approval Austria: 14.09.2023 (BASG) und 10.10.2023 (IEC Wien) Approval Serbia: 14.02.2025 (Serbian Agency for Medicines and Medical Devices, including IEC)</p> <ul style="list-style-type: none"> • Adjustment of recruitment period and study duration • Non-implementation of interim evaluation • Change in key secondary endpoints (and the resulting change in the evaluation method) • 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>