Clinical trial results:
A Multinational Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults With Pulmonary Arterial Hypertension (PAH)

Summary

EudraCT number	2013-004362-34
Trial protocol	SE AT BE DE ES CZ RO PL GR NL PT HR LV
Global end of trial date	26 February 2021

Results information

Result version number	v2 (current)
This version publication date	17 July 2022
First version publication date	18 April 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	A1481324

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02060487
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Viatris Specialty LLC
Sponsor organisation address	3711 Collins Ferry Road, Morgantown, United States, WV 26505
Public contact	Global Clinical Operations Lead, Meda Pharma GmbH & Co. KG (A Viatris company), Baerbel.Fingerhut@viatris.com
Scientific contact	Global Clinical Operations Lead, Meda Pharma GmbH & Co. KG (A Viatris company), Baerbel.Fingerhut@viatris.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 February 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To test for the non-inferiority of sildenafil 80 milligrams (mg) versus 5 mg for mortality; mortality rate with the 80 mg dose was to be no worse than double the mortality rate for the 5 mg dose.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 September 2014
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	Australia: 7
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Bosnia and Herzegovina: 13
Country: Number of subjects enrolled	Croatia: 10
Country: Number of subjects enrolled	Czechia: 37
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Latvia: 20
Country: Number of subjects enrolled	Malaysia: 17
Country: Number of subjects enrolled	Mexico: 9
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Romania: 29
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Serbia: 14
Country: Number of subjects enrolled	Singapore: 4
Country: Number of subjects enrolled	South Africa: 3
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Thailand: 28

Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Ukraine: 68
Country: Number of subjects enrolled	United States: 10
Worldwide total number of subjects	385
EEA total number of subjects	150

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)	291
From 65 to 84 years	94
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomised, double-blind, parallel-group, multinational and multicenter study to assess the effects of oral sildenafil on mortality in adult subjects with pulmonary arterial hypertension (PAH). The study was conducted at 68 active sites in 23 countries.

Pre-assignment

Screening details:

A total of 445 subjects were screened of which, 47 subjects failed screening and 13 subjects were neither screen failures nor randomised. A total of 385 subjects were actually enrolled into the study and assigned to a study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Sildenafil 5 mg

Arm description:

Subjects received a single tablet of sildenafil at a dose of 5 milligram (mg) along with two tablets of placebo matching 20 mg and 80 mg sildenafil orally thrice daily (TID) until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2080 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Arm type	Experimental
Investigational medicinal product name	Sildenafil citrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single tablet of sildenafil at a dose of 5 mg orally thrice daily (TID).

Investigational medicinal product name	80 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 80 mg orally TID.

Investigational medicinal product name	20 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 20 mg orally TID.

Arm title	Sildenafil 20 mg

Arm description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo

matching 5 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 1984 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Arm type	Experimental
Investigational medicinal product name	Sildenafil citrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single tablet of sildenafil at a dose of 20 mg orally TID

Investigational medicinal product name	80 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 80 mg orally TID

Investigational medicinal product name	5 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 5 mg orally TID.

Arm title	Sildenafil 80 mg

Arm description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID on day 1 for 2 weeks and then titrated up to 80 mg at week 2 along with two tablets of placebo matching 5 mg and 20 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2073 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Arm type	Experimental
Investigational medicinal product name	5 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single tablet of placebo at a dose of 5 mg orally TID.

Investigational medicinal product name	Sildenafil citrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single tablet of sildenafil at a dose of 80 mg orally TID

Investigational medicinal product name	20 mg matching placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Subjects received a single tablet of placebo at a dose of 5 mg orally TID.

Number of subjects in period 1	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg
Started	129	128	128
Completed	0	0	0
Not completed	129	128	128
Consent withdrawn by subject	3	10	4
Study Terminated By Sponsor	87	89	100
Adverse event, non-fatal	-	-	1
Death	34	25	19
Unspecified	1	2	1
Lost to follow-up	3	-	2
Randomised in error	1	-	-
Lack of efficacy	-	1	-
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Sildenafil 5 mg
Reporting group description:	
Subjects received a single tablet of sildenafil at a dose of 5 milligram (mg) along with two tablets of placebo matching 20 mg and 80 mg sildenafil orally thrice daily (TID) until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2080 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.	
Reporting group title	Sildenafil 20 mg
Reporting group description:	
Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 1984 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.	
Reporting group title	Sildenafil 80 mg
Reporting group description:	
Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID on day 1 for 2 weeks and then titrated up to 80 mg at week 2 along with two tablets of placebo matching 5 mg and 20 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2073 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.	

Reporting group values	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg
Number of subjects	129	128	128
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)	98	98	95
From 65-84 years	31	30	33
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	51.4	51.2	52.1
standard deviation	± 15.02	± 15.81	± 14.72
Sex: Female, Male Units: Subjects			
Female	97	102	98
Male	32	26	30
Race Units: Subjects			
Asian	23	14	19
White	104	113	108
Unknown or Not Reported	2	1	1
Ethnicity			

Units: Subjects			
Hispanic or Latino	5	4	3
Not Hispanic or Latino	124	124	125

Reporting group values	Total		
Number of subjects	385		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	291		
From 65-84 years	94		
85 years and over	0		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	297		
Male	88		
Race Units: Subjects			
Asian	56		
White	325		
Unknown or Not Reported	4		
Ethnicity Units: Subjects			
Hispanic or Latino	12		
Not Hispanic or Latino	373		

End points

End points reporting groups

Reporting group title	Sildenafil 5 mg

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 5 milligram (mg) along with two tablets of placebo matching 20 mg and 80 mg sildenafil orally thrice daily (TID) until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2080 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Reporting group title	Sildenafil 20 mg

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 1984 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Reporting group title	Sildenafil 80 mg

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID on day 1 for 2 weeks and then titrated up to 80 mg at week 2 along with two tablets of placebo matching 5 mg and 20 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2073 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Primary: Overall Survival

End point title	Overall Survival

End point description:

In this end point number of deaths during the study were reported. The intent-to-treat population (ITT) included all randomised subjects treated with study treatment.

End point type	Primary

End point timeframe:

Day 1 of study treatment up to date of death (within a maximum duration of 2102 days)

End point values	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	128	128	
Units: Subjects	34	25	19	

Statistical analyses

Statistical analysis title	Sildenafil 20 mg versus Sildenafil 5 mg TID

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

Comparison groups	Sildenafil 5 mg v Sildenafil 20 mg

Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	Other: 99.7 %
sides	2-sided
lower limit	0.31
upper limit	1.49

Notes:

[1] - Non-inferiority of sildenafil 20 mg TID versus sildenafil 5 mg TID was to be concluded if the upper limit of the 99.7% confidence interval (CI) for hazard ratio (HR) was less than 2.

Statistical analysis title	Sildenafil 80 mg versus Sildenafil 5 mg TID

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

Comparison groups	Sildenafil 5 mg v Sildenafil 80 mg
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.51
Confidence interval	
level	Other: 99.7 %
sides	2-sided
lower limit	0.22
upper limit	1.21

Notes:

[2] - Non-inferiority of sildenafil 80 mg TID vs. sildenafil 5 mg TID was to be concluded if the upper limit of the 99.7% CI for HR was less than 2.

Statistical analysis title	Sildenafil 80 mg versus Sildenafil 20 mg TID

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

Comparison groups	Sildenafil 20 mg v Sildenafil 80 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	Other: 99.7 %
sides	2-sided
lower limit	0.3
upper limit	1.84

Notes:

[3] - Non-inferiority of sildenafil 80 mg TID vs. sildenafil 20 mg TID was to be concluded if the upper limit of the 99.7% CI for HR is less than 2.

Secondary: Number of Subjects With Clinical Worsening Events

End point title	Number of Subjects With Clinical Worsening Events

End point description:

Clinical worsening was defined as all-cause mortality, non-elective hospital stay for worsening pulmonary arterial hypertension (PAH) (including but not limited to right heart failure [RHF], initiation of intravenous (IV) prostanoids, lung transplantation, or septostomy) or disease progression. Disease progression was defined as a reduction from baseline in the 6-Minute Walk Distance (6MWD) test by 15% and worsening functional class from baseline, both confirmed by second test within 2 weeks of study treatment. ITT population included all randomised subjects treated with study treatment.

End point type	Secondary

End point timeframe:

Day 1 of study treatment up to date of clinical worsening event (within a maximum duration of 2080 days)

End point values	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	129	128	128	
Units: Subjects	52	36	28	

Statistical analyses

Statistical analysis title	Sildenafil 20 mg versus Sildenafil 5 mg TID

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

Comparison groups	Sildenafil 5 mg v Sildenafil 20 mg
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.035
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	Other: 99.7 %
sides	2-sided
lower limit	0.33
upper limit	1.21

Statistical analysis title	Sildenafil 80 mg versus Sildenafil 5 mg TID

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

Comparison groups	Sildenafil 5 mg v Sildenafil 80 mg

Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.44
Confidence interval	
level	Other: 99.7 %
sides	2-sided
lower limit	0.22
upper limit	0.89

Statistical analysis title	Sildenafil 80 mg versus Sildenafil 20 mg TID

Statistical analysis description:

Hazard ratio estimated from the Proportional Hazards model, stratified by actual previous PAH treatment and etiology of PAH.

Comparison groups	Sildenafil 20 mg v Sildenafil 80 mg
Number of subjects included in analysis	256
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.195
Method	Wald test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	Other: 99.7 %
sides	2-sided
lower limit	0.34
upper limit	1.52

Secondary: Change From Baseline in 6-Minute Walk Distance (6MWD) at Month 6

End point title	Change From Baseline in 6-Minute Walk Distance (6MWD) at Month 6

End point description:

6MWD was the distance that a subject could walk in 6 minutes. Subjects were asked to perform the test at a pace that was comfortable to them, with as many breaks as they needed. Analysis was performed using mixed model for repeated measures (MMRM), adjusted for baseline 6MWD and for randomisation stratification factors: PAH treatment at study entry and etiology of PAH. ITT population included all randomised subjects treated with study treatment. Here, "overall number of subjects analysed" signifies number of subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 6

End point values	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	113	118	116	
Units: Meters				
least squares mean (confidence interval 95%)	12.2 (-0.67 to 25.16)	27.3 (14.52 to 39.99)	31.2 (18.68 to 43.66)	

Statistical analyses

Statistical analysis title	Sildenafil 20 mg versus Sildenafil 5 mg TID
Comparison groups	Sildenafil 5 mg v Sildenafil 20 mg
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0627
Method	MMRM
Parameter estimate	Least-squares means difference
Point estimate	15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	30.81

Statistical analysis title	Sildenafil 80 mg versus Sildenafil 20 mg TID
Comparison groups	Sildenafil 20 mg v Sildenafil 80 mg
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6254
Method	MMRM
Parameter estimate	Least-squares means difference
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.85
upper limit	19.68

Statistical analysis title	Sildenafil 80 mg versus Sildenafil 5 mg TID
Comparison groups	Sildenafil 5 mg v Sildenafil 80 mg

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0201
Method	MMRM
Parameter estimate	Least-squares means difference
Point estimate	18.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.99
upper limit	34.86

Secondary: Change From Baseline in 6-Minute Walk Distance (6MWD) at Month 12

End point title	Change From Baseline in 6-Minute Walk Distance (6MWD) at Month 12

End point description:

6MWD was the distance that a subject could walk in 6 minutes. Participants were asked to perform the test at a pace that was comfortable to them, with as many breaks as they needed. Analysis was performed using mixed model for repeated measures (MMRM), adjusted for baseline 6MWD and for randomization stratification factors: PAH treatment at study entry and etiology of PAH. ITT population included all randomised subjects treated with study treatment. Here, "overall number of subjects analysed" signifies number of subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Month 12

End point values	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	88	89	89	
Units: Meters				
least squares mean (confidence interval 95%)	14.3 (-0.58 to 29.27)	35.7 (20.91 to 50.48)	34.8 (20.21 to 49.43)	

Statistical analyses

Statistical analysis title	Sildenafil 20 mg versus Sildenafil 5 mg TID
Comparison groups	Sildenafil 5 mg v Sildenafil 20 mg
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0286
Method	MMRM
Parameter estimate	Least-squares means difference
Point estimate	21.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.25
upper limit	40.45

Statistical analysis title	Sildenafil 80 mg versus Sildenafil 5 mg TID
Comparison groups	Sildenafil 5 mg v Sildenafil 80 mg
Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0364
Method	MMRM
Parameter estimate	Least-squares means difference
Point estimate	20.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	39.65

Statistical analysis title	Sildenafil 80 mg versus Sildenafil 20 mg TID
Comparison groups	Sildenafil 20 mg v Sildenafil 80 mg
Number of subjects included in analysis	178
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9283
Method	MMRM
Parameter estimate	Least-squares means difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.94
upper limit	18.19

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose of study treatment (up to a maximum duration of 2108 days for sildenafil 5 mg; up to a maximum duration of 2012 days for sildenafil 20 mg; up to a maximum duration of 2101 days for sildenafil 80 mg)

Adverse event reporting additional description:

An AE term may be reported as both a serious and non-serious AE, but are distinct events. An AE may be serious for 1 subject and non-serious for another subject, or a subject may have experienced both a serious and non-serious episode of the same event. Safety population comprised of all randomised subjects treated with study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Sildenafil 5 mg

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 5 mg along with two tablets of placebo matching 20 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2080 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Reporting group title	Sildenafil 20 mg

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 1984 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Reporting group title	Sildenafil 80 mg

Reporting group description:

Subjects received a single tablet of sildenafil at a dose of 20 mg along with two tablets of placebo matching 5 mg and 80 mg sildenafil orally TID on day 1 for 2 weeks and then titrated up to 80 mg at week 2 along with two tablets of placebo matching 5 mg and 20 mg sildenafil orally TID until discontinuation of study treatment or end of study. The maximum duration of study treatment was 2073 days approximately. Subjects were followed up for at least 28 days after last dose of study treatment.

Serious adverse events	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 129 (51.16%)	49 / 128 (38.28%)	51 / 128 (39.84%)
number of deaths (all causes)	34	25	19
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal carcinoma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelofibrosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleomorphic malignant fibrous histiocytoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural neoplasm			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

Aortic stenosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose ulceration			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Drug therapy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hospitalisation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung transplant			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Disease progression			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Exercise tolerance decreased			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	3 / 129 (2.33%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 0
Vascular stent stenosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Ovarian cyst ruptured			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alveolitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 27	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 129 (2.33%)	1 / 128 (0.78%)	4 / 128 (3.13%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperventilation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	17 / 129 (13.18%)	10 / 128 (7.81%)	8 / 128 (6.25%)
occurrences causally related to treatment / all	0 / 23	0 / 16	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	2 / 129 (1.55%)	4 / 128 (3.13%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory disorder			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	3 / 129 (2.33%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic sclerosis pulmonary			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vocal cord dysfunction			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Delusion			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Haemodynamic test			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemoglobin decreased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural intestinal perforation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Thoracic vertebral fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyarrhythmia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 129 (0.78%)	3 / 128 (2.34%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	9 / 129 (6.98%)	8 / 128 (6.25%)	3 / 128 (2.34%)
occurrences causally related to treatment / all	0 / 10	0 / 9	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure acute			

subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	1 / 5	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	3 / 128 (2.34%)
occurrences causally related to treatment / all	0 / 8	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiovascular insufficiency			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	11 / 129 (8.53%)	4 / 128 (3.13%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 16	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular extrasystoles			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia paroxysmal			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypochromic anaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis mesenteric vessel			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal vein thrombosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Hypersensitivity vasculitis			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasculitic rash			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 129 (3.10%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal failure			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthropathy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Connective tissue disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oligoarthritis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporotic fracture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Rheumatic disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scleroderma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	3 / 128 (2.34%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	3 / 128 (2.34%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella bacteraemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leptospirosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			

subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis chronic			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	7 / 129 (5.43%)	6 / 128 (4.69%)	3 / 128 (2.34%)
occurrences causally related to treatment / all	0 / 10	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Septic shock			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcal bacteraemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Cachexia			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Sildenafil 5 mg	Sildenafil 20 mg	Sildenafil 80 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 129 (83.72%)	107 / 128 (83.59%)	111 / 128 (86.72%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma stage IV			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Basal cell carcinoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Benign pancreatic neoplasm			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Bowen's disease			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Breast cancer			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Haemangioma of bone			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Haemangioma of liver			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	2
Lipoma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Malignant melanoma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Melanocytic naevus			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Myelofibrosis			

subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Myeloproliferative neoplasm			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Polycythaemia vera			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Rectal neoplasm			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Skin papilloma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Uterine leiomyoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	3	0	2
Cyanosis			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	2	1	1
Deep vein thrombosis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Flushing			
subjects affected / exposed	6 / 129 (4.65%)	3 / 128 (2.34%)	4 / 128 (3.13%)
occurrences (all)	6	5	4
Haematoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	2
Haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0

Hot flush			
subjects affected / exposed	0 / 129 (0.00%)	3 / 128 (2.34%)	2 / 128 (1.56%)
occurrences (all)	0	3	3
Hyperaemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	2 / 129 (1.55%)	6 / 128 (4.69%)	5 / 128 (3.91%)
occurrences (all)	2	9	5
Hypertensive crisis			
subjects affected / exposed	3 / 129 (2.33%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	3	0	0
Hypotension			
subjects affected / exposed	9 / 129 (6.98%)	6 / 128 (4.69%)	7 / 128 (5.47%)
occurrences (all)	11	6	15
Jugular vein thrombosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Labile blood pressure			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Lymphoedema			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Neovascularisation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Peripheral venous disease			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Phlebitis			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	2	1	0

Raynaud's phenomenon			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Thrombophlebitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Varicose vein			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Vasodilatation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Cancer surgery			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Cardiac ablation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Cataract operation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	3 / 128 (2.34%)
occurrences (all)	0	2	4
Dental operation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Haematoma evacuation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Myomectomy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Tooth extraction			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	2	1
Tooth repair			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Vascular operation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 129 (2.33%)	7 / 128 (5.47%)	2 / 128 (1.56%)
occurrences (all)	3	14	3
Catheter site erythema			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Chest discomfort			
subjects affected / exposed	3 / 129 (2.33%)	3 / 128 (2.34%)	0 / 128 (0.00%)
occurrences (all)	11	6	0
Chest pain			
subjects affected / exposed	7 / 129 (5.43%)	15 / 128 (11.72%)	13 / 128 (10.16%)
occurrences (all)	9	30	72
Chills			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	5 / 128 (3.91%)
occurrences (all)	2	1	5
Crying			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Cyst			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	3
Disease progression			
subjects affected / exposed	3 / 129 (2.33%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	3	0	0
Face oedema			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Facial pain			

subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	11 / 129 (8.53%)	10 / 128 (7.81%)	9 / 128 (7.03%)
occurrences (all)	19	17	18
Feeling cold			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	4	1	0
Feeling hot			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	16	2	0
Gait disturbance			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
General physical health deterioration			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Generalised oedema			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Ill-defined disorder			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Inflammation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Influenza like illness			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Infusion site pain			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Injection site hypersensitivity			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Malaise			

subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	3	1
Mucosal dryness			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	3 / 128 (2.34%)
occurrences (all)	5	2	4
Oedema peripheral			
subjects affected / exposed	14 / 129 (10.85%)	17 / 128 (13.28%)	8 / 128 (6.25%)
occurrences (all)	18	25	9
Pain			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	3 / 128 (2.34%)
occurrences (all)	3	3	3
Peripheral swelling			
subjects affected / exposed	7 / 129 (5.43%)	6 / 128 (4.69%)	5 / 128 (3.91%)
occurrences (all)	9	6	7
Pyrexia			
subjects affected / exposed	3 / 129 (2.33%)	9 / 128 (7.03%)	9 / 128 (7.03%)
occurrences (all)	3	11	15
Swelling			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Swelling face			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Ulcer			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site bruise			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Vessel puncture site haematoma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			

Allergy to arthropod bite			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Drug hypersensitivity			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Food allergy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Hypersensitivity			
subjects affected / exposed	2 / 129 (1.55%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	3	2	1
Multiple allergies			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Seasonal allergy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Secondary immunodeficiency			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Amenorrhoea			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Breast cyst			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	2
Breast inflammation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Breast mass			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Breast pain			

subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Dysmenorrhoea			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	6	1
Endometriosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Gynaecomastia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Menorrhagia			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Menstrual disorder			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Ovarian cyst			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Priapism			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Uterine polyp			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Vaginal haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	3	1
Vulvovaginal pruritus			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal			

disorders			
Alveolitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Asthma			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	0	1	3
Bronchial hyperreactivity			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Bronchitis chronic			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	0	1	2
Bronchopneumopathy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Catarrh			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	0	1	4
Chronic respiratory failure			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	14 / 129 (10.85%)	11 / 128 (8.59%)	12 / 128 (9.38%)
occurrences (all)	24	14	25
Dysphonia			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	3	1	0
Dyspnoea			
subjects affected / exposed	12 / 129 (9.30%)	16 / 128 (12.50%)	11 / 128 (8.59%)
occurrences (all)	15	35	16
Dyspnoea exertional			

subjects affected / exposed	1 / 129 (0.78%)	3 / 128 (2.34%)	0 / 128 (0.00%)
occurrences (all)	1	4	0
Emphysema			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	11 / 129 (8.53%)	13 / 128 (10.16%)	13 / 128 (10.16%)
occurrences (all)	12	21	22
Haemoptysis			
subjects affected / exposed	1 / 129 (0.78%)	3 / 128 (2.34%)	1 / 128 (0.78%)
occurrences (all)	2	3	1
Hiccups			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Hyperventilation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Hypoxia			
subjects affected / exposed	0 / 129 (0.00%)	3 / 128 (2.34%)	0 / 128 (0.00%)
occurrences (all)	0	4	0
Idiopathic pulmonary fibrosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Increased upper airway secretion			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Interstitial lung disease			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Lung disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Lung infiltration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			

subjects affected / exposed	8 / 129 (6.20%)	4 / 128 (3.13%)	5 / 128 (3.91%)
occurrences (all)	10	6	5
Nasal dryness			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	2 / 129 (1.55%)	6 / 128 (4.69%)	2 / 128 (1.56%)
occurrences (all)	2	11	3
Paranasal sinus discomfort			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Pharyngeal swelling			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Pleural effusion			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Pleurisy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Pleuritic pain			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	1	2	1
Prolonged expiration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Pulmonary arterial hypertension			
subjects affected / exposed	10 / 129 (7.75%)	7 / 128 (5.47%)	4 / 128 (3.13%)
occurrences (all)	15	8	7
Pulmonary embolism			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Pulmonary fibrosis			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Pulmonary hypertension			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Pulmonary vascular disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Rales			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Respiratory disorder			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	4	0	0
Respiratory failure			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	2	1	1
Rhinitis allergic			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	1	2	0
Rhinorrhoea			
subjects affected / exposed	2 / 129 (1.55%)	4 / 128 (3.13%)	3 / 128 (2.34%)
occurrences (all)	2	5	3
Rhonchi			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Sinonasal obstruction			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Sinus congestion			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Sneezing			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Throat irritation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	0	1	3
Vasomotor rhinitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Vocal cord polyp			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Wheezing			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	3	2	1
Apathy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Confusional state			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Depressed mood			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Depression			
subjects affected / exposed	1 / 129 (0.78%)	3 / 128 (2.34%)	1 / 128 (0.78%)
occurrences (all)	1	3	1
Emotional disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0

Initial insomnia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	4 / 129 (3.10%)	5 / 128 (3.91%)	2 / 128 (1.56%)
occurrences (all)	27	6	2
Mental disorder			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Mood altered			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Mood swings			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Nervousness			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Sleep disorder			
subjects affected / exposed	2 / 129 (1.55%)	3 / 128 (2.34%)	1 / 128 (0.78%)
occurrences (all)	5	3	1
Product issues			
Device breakage			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Device fastener issue			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Biliary dilatation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Biliary dyskinesia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Cardiac cirrhosis			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Cholecystitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Cholecystocholangitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Cholelithiasis			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	4	3	1
Congestive hepatopathy			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Hepatic cirrhosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Hepatic function abnormal			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Hepatic steatosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Hepatitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Hepatomegaly			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	2
Hepatosplenomegaly			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Hyperbilirubinaemia			
subjects affected / exposed	3 / 129 (2.33%)	4 / 128 (3.13%)	0 / 128 (0.00%)
occurrences (all)	3	4	0
Liver disorder			

subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Ocular icterus			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	1	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Blood albumin abnormal			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	1	1	1
Blood bilirubin increased			
subjects affected / exposed	3 / 129 (2.33%)	3 / 128 (2.34%)	3 / 128 (2.34%)
occurrences (all)	7	3	3
Blood cholesterol increased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	1	1	1
Blood glucose decreased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Blood iron decreased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Blood potassium abnormal			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Blood pressure decreased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	0	4	2
Blood pressure diastolic decreased			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	2	1	1
Blood pressure increased			
subjects affected / exposed	3 / 129 (2.33%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	12	1	2
Blood pressure measurement			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	1	1	1
Blood uric acid increased			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	2 / 128 (1.56%)
occurrences (all)	0	2	2
Body temperature increased			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	9	1
Breath sounds abnormal			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Colonoscopy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Endoscopy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Fibrin D dimer increased			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Haemodynamic test			

subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Heart rate			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Heart rate decreased			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Heart rate increased			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Heart sounds abnormal			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Liver function test abnormal			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Oxygen saturation decreased			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Protein total abnormal			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
SARS-CoV-2 test positive			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Staphylococcus test positive			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Transaminases increased			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Troponin increased			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Ultrasound scan			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Venous pressure jugular increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Vitamin D decreased			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Walking distance test abnormal			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	3	0	0
Weight decreased			
subjects affected / exposed	4 / 129 (3.10%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	7	1	2
Weight increased			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	2	1	1
White blood cell count increased			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	0	1	2
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	3	1
Arthropod sting			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Back injury			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Burn oral cavity			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Chest injury			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Contusion			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	1	2	1
Endotracheal intubation complication			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Epicondylitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Exposure via breast milk			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Facial bones fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	4 / 129 (3.10%)	2 / 128 (1.56%)	3 / 128 (2.34%)
occurrences (all)	4	2	5
Head injury			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	2	1
Humerus fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Ligament sprain			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Limb injury			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Lower limb fracture			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Muscle injury			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Muscle rupture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Muscle strain			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	1	1	2
Nasal injury			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Oral contusion			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Rib fracture			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	2	1
Road traffic accident			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Scar			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Skin laceration			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Soft tissue injury			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Thermal burn			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Tooth fracture			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	2	1	0
Upper limb fracture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	2 / 129 (1.55%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	2	2	1
Thyroid malformation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Angina pectoris			
subjects affected / exposed	0 / 129 (0.00%)	4 / 128 (3.13%)	2 / 128 (1.56%)
occurrences (all)	0	8	3
Arrhythmia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	3
Atrial fibrillation			

subjects affected / exposed	2 / 129 (1.55%)	3 / 128 (2.34%)	2 / 128 (1.56%)
occurrences (all)	2	4	2
Atrial flutter			
subjects affected / exposed	3 / 129 (2.33%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	4	1	1
Atrial thrombosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Atrioventricular block first degree			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Bradycardia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Cardiac failure			
subjects affected / exposed	3 / 129 (2.33%)	0 / 128 (0.00%)	3 / 128 (2.34%)
occurrences (all)	3	0	4
Cardiac failure acute			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Cardiac failure congestive			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	1	2	1
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Coronary artery stenosis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Extrasystoles			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	5 / 129 (3.88%)	5 / 128 (3.91%)	6 / 128 (4.69%)
occurrences (all)	6	6	19
Pericardial effusion			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	3	1
Right ventricular dysfunction			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Right ventricular failure			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	3	2	0
Supraventricular extrasystoles			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	3	0	0
Supraventricular tachycardia			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	2 / 129 (1.55%)	2 / 128 (1.56%)	5 / 128 (3.91%)
occurrences (all)	3	7	5
Tricuspid valve incompetence			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Ventricular extrasystoles			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	2	0	2
Ventricular tachycardia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Ageusia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Amnesia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Anosmia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1

Aphasia			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Balance disorder			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Burning sensation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Carpal tunnel syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Cerebral atrophy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Cervical radiculopathy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Cognitive disorder			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Diabetic neuropathy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Dizziness			
subjects affected / exposed	12 / 129 (9.30%)	15 / 128 (11.72%)	18 / 128 (14.06%)
occurrences (all)	17	21	30
Dizziness exertional			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	4	0
Encephalopathy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Epilepsy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0

Head discomfort			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Headache			
subjects affected / exposed	26 / 129 (20.16%)	45 / 128 (35.16%)	33 / 128 (25.78%)
occurrences (all)	105	106	95
Hypoaesthesia			
subjects affected / exposed	2 / 129 (1.55%)	3 / 128 (2.34%)	2 / 128 (1.56%)
occurrences (all)	3	5	2
Hypotonia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Intercostal neuralgia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Lethargy			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Loss of consciousness			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Migraine			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	10	0
Neuralgia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Neuritis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	2 / 129 (1.55%)	3 / 128 (2.34%)	2 / 128 (1.56%)
occurrences (all)	3	4	3
Postictal paralysis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0

Presyncope			
subjects affected / exposed	1 / 129 (0.78%)	4 / 128 (3.13%)	1 / 128 (0.78%)
occurrences (all)	1	6	1
Radiculopathy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Sciatica			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Sensory loss			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Sinus headache			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	4
Somnolence			
subjects affected / exposed	3 / 129 (2.33%)	5 / 128 (3.91%)	0 / 128 (0.00%)
occurrences (all)	4	7	0
Syncope			
subjects affected / exposed	4 / 129 (3.10%)	4 / 128 (3.13%)	4 / 128 (3.13%)
occurrences (all)	6	10	5
Tension headache			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	3 / 128 (2.34%)
occurrences (all)	0	0	4
Trigeminal neuralgia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Trigeminal neuritis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Vascular encephalopathy			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 129 (3.88%)	3 / 128 (2.34%)	11 / 128 (8.59%)
occurrences (all)	6	3	15
Bicytopenia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Blood loss anaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Cytopenia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Heparin-induced thrombocytopenia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Hypothrombinaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Increased tendency to bruise			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Leukopenia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Lymphadenopathy			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	2	1
Lymphocytosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Macrocytosis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Pancytopenia			

subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Polycythaemia			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Splenomegaly			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Thrombocytopenia			
subjects affected / exposed	2 / 129 (1.55%)	2 / 128 (1.56%)	3 / 128 (2.34%)
occurrences (all)	2	2	3
Lymphadenitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Iron deficiency anaemia			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	3 / 128 (2.34%)
occurrences (all)	2	0	3
Ear and labyrinth disorders			
Cerumen impaction			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Ear congestion			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Ear haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	5
Ear pain			
subjects affected / exposed	1 / 129 (0.78%)	3 / 128 (2.34%)	1 / 128 (0.78%)
occurrences (all)	1	3	1
Hypoacusis			
subjects affected / exposed	3 / 129 (2.33%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	4	2	0
Mixed deafness			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0

Tinnitus			
subjects affected / exposed	1 / 129 (0.78%)	4 / 128 (3.13%)	1 / 128 (0.78%)
occurrences (all)	1	6	1
Vertigo			
subjects affected / exposed	2 / 129 (1.55%)	4 / 128 (3.13%)	2 / 128 (1.56%)
occurrences (all)	2	4	2
Eye disorders			
Asthenopia			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Astigmatism			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Blepharitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	4 / 129 (3.10%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	4	0	2
Chalazion			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Chromatopsia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Conjunctival haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	4	1
Cornea verticillata			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Corneal oedema			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Corneal opacity			

subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Dacryostenosis acquired			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Dark circles under eyes			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Diplopia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Dry eye			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	1	1	1
Dyschromatopsia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Eye disorder			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	2	1	0
Eye haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Eye inflammation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Eye irritation			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Eye pain			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	3 / 128 (2.34%)
occurrences (all)	0	0	6
Eye pruritus			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Eye swelling			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Foreign body sensation in eyes			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	5	0
Glaucoma			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Hypermetropia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Keratitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Lacrimation increased			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Macular degeneration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Maculopathy			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	2
Periorbital pain			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Periorbital swelling			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	3	1
Photophobia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Photopsia			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Pterygium			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Retinal vascular disorder			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	2	1
Swelling of eyelid			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Vision blurred			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	2 / 128 (1.56%)
occurrences (all)	3	3	2
Visual impairment			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	4 / 128 (3.13%)
occurrences (all)	1	2	5
Visual snow syndrome			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Xerophthalmia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	2	1	0
Abdominal distension			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	2 / 128 (1.56%)
occurrences (all)	2	2	2
Abdominal pain			
subjects affected / exposed	5 / 129 (3.88%)	5 / 128 (3.91%)	4 / 128 (3.13%)
occurrences (all)	8	12	6
Abdominal pain lower			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0

Abdominal pain upper			
subjects affected / exposed	6 / 129 (4.65%)	7 / 128 (5.47%)	11 / 128 (8.59%)
occurrences (all)	12	29	15
Abdominal symptom			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Angular cheilitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Ascites			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	3	2	1
Barrett's oesophagus			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Chronic gastritis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Colitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Constipation			
subjects affected / exposed	5 / 129 (3.88%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	5	1	1
Dental necrosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	13 / 129 (10.08%)	17 / 128 (13.28%)	20 / 128 (15.63%)
occurrences (all)	27	45	28
Diverticulum intestinal			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Dry mouth			
subjects affected / exposed	0 / 129 (0.00%)	3 / 128 (2.34%)	3 / 128 (2.34%)
occurrences (all)	0	4	3

Duodenal bulb deformity			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Duodenal ulcer			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Duodenal vascular ectasia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Duodenogastric reflux			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Dyspepsia			
subjects affected / exposed	6 / 129 (4.65%)	10 / 128 (7.81%)	10 / 128 (7.81%)
occurrences (all)	8	12	24
Dysphagia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Enteritis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Enterocolitis			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	3	0	1
Epigastric discomfort			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	3	0	1
Eructation			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Faeces discoloured			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	4	0

Food poisoning			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	3 / 128 (2.34%)
occurrences (all)	1	2	4
Frequent bowel movements			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Gastric disorder			
subjects affected / exposed	0 / 129 (0.00%)	3 / 128 (2.34%)	1 / 128 (0.78%)
occurrences (all)	0	13	1
Gastric polyps			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Gastritis			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	3 / 128 (2.34%)
occurrences (all)	3	2	3
Gastritis erosive			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	4 / 128 (3.13%)
occurrences (all)	1	2	5
Gingival bleeding			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Gingival hypertrophy			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Gingival pain			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1

Haematochezia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	2	0
Haemorrhoids			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	2
Hiatus hernia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Hypoaesthesia oral			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	0	0	3
Intestinal haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Intestinal polyp			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Irritable bowel syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Large intestine polyp			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	1	0	2
Mouth haemorrhage			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	2
Mouth ulceration			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	16 / 129 (12.40%)	12 / 128 (9.38%)	8 / 128 (6.25%)
occurrences (all)	17	20	12

Odynophagia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Oesophageal disorder			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Pancreatitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	0	1	2
Peptic ulcer			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Rectal haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Stomatitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Tongue erythema			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Tongue ulceration			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	5 / 129 (3.88%)	5 / 128 (3.91%)	3 / 128 (2.34%)
occurrences (all)	5	5	3
Umbilical hernia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Varices oesophageal			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0

Vomiting			
subjects affected / exposed	7 / 129 (5.43%)	10 / 128 (7.81%)	7 / 128 (5.47%)
occurrences (all)	11	14	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 129 (0.00%)	3 / 128 (2.34%)	0 / 128 (0.00%)
occurrences (all)	0	3	0
Chronic spontaneous urticaria			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Dermatitis allergic			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	3 / 128 (2.34%)
occurrences (all)	0	0	3
Dermatitis atopic			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Diabetic foot			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Eczema nummular			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	2 / 129 (1.55%)	4 / 128 (3.13%)	4 / 128 (3.13%)
occurrences (all)	31	7	5
Hyperhidrosis			
subjects affected / exposed	2 / 129 (1.55%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	3	2	0
Hypersensitivity vasculitis			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Photosensitivity reaction			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	4 / 129 (3.10%)	3 / 128 (2.34%)	3 / 128 (2.34%)
occurrences (all)	5	3	3
Rash			
subjects affected / exposed	3 / 129 (2.33%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	7	1	3
Rash erythematous			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Rash macular			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	1	1	1
Rash papular			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Skin burning sensation			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Skin disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Skin fissures			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Skin hyperpigmentation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Skin irritation			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Skin lesion			

subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	2	2	2
Telangiectasia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Vitiligo			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Yellow skin			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Azotaemia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Chronic kidney disease			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Dysuria			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Haematuria			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	3	0
Proteinuria			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Pyelocaliectasis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0

Renal cyst			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	3 / 128 (2.34%)
occurrences (all)	3	1	3
Renal failure			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	1	2	3
Renal impairment			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	1	1	2
Urinary retention			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Autoimmune thyroiditis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Cushing's syndrome			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Hyperthyroidism			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Hypothyroidism			
subjects affected / exposed	2 / 129 (1.55%)	4 / 128 (3.13%)	2 / 128 (1.56%)
occurrences (all)	2	4	2
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Primary hypothyroidism			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Thyroid mass			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	14 / 129 (10.85%)	13 / 128 (10.16%)	15 / 128 (11.72%)
occurrences (all)	17	19	24
Arthritis			
subjects affected / exposed	3 / 129 (2.33%)	3 / 128 (2.34%)	0 / 128 (0.00%)
occurrences (all)	3	4	0
Back pain			
subjects affected / exposed	16 / 129 (12.40%)	10 / 128 (7.81%)	14 / 128 (10.94%)
occurrences (all)	20	24	23
Bone pain			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	0	6	1
Bursitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Gouty arthritis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	2	1	2
Limb mass			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Metatarsalgia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Muscle contracture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	4 / 129 (3.10%)	3 / 128 (2.34%)	3 / 128 (2.34%)
occurrences (all)	5	5	5
Muscular weakness			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	1	2	0

Musculoskeletal discomfort			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	4 / 129 (3.10%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	4	0	0
Musculoskeletal stiffness			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	3	1
Myalgia			
subjects affected / exposed	4 / 129 (3.10%)	10 / 128 (7.81%)	12 / 128 (9.38%)
occurrences (all)	5	16	17
Neck pain			
subjects affected / exposed	0 / 129 (0.00%)	3 / 128 (2.34%)	4 / 128 (3.13%)
occurrences (all)	0	4	4
Osteitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Osteoarthritis			
subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	3 / 128 (2.34%)
occurrences (all)	1	3	3
Osteochondrosis			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	4 / 128 (3.13%)
occurrences (all)	2	1	4
Osteopenia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Osteoporosis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Osteoporotic fracture			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0

Pain in extremity			
subjects affected / exposed	6 / 129 (4.65%)	14 / 128 (10.94%)	6 / 128 (4.69%)
occurrences (all)	7	17	13
Pain in jaw			
subjects affected / exposed	3 / 129 (2.33%)	3 / 128 (2.34%)	1 / 128 (0.78%)
occurrences (all)	3	3	2
Pathological fracture			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Plantar fasciitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Polymyalgia rheumatica			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Rheumatoid arthritis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Sclerodactylia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Scleroderma			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Sjogren's syndrome			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Spinal disorder			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Spinal pain			
subjects affected / exposed	1 / 129 (0.78%)	3 / 128 (2.34%)	0 / 128 (0.00%)
occurrences (all)	2	4	0
Systemic lupus erythematosus			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1

Systemic scleroderma			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	3	0
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Tendonitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	3	0
Trigger finger			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Undifferentiated connective tissue disease			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Acute sinusitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	3 / 128 (2.34%)
occurrences (all)	1	0	3
Bacterial disease carrier			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Bacterial infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Bacterial rhinitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	11 / 129 (8.53%)	11 / 128 (8.59%)	8 / 128 (6.25%)
occurrences (all)	16	11	8
Bronchitis viral			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
COVID-19 pneumonia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	3	2	1
Chronic sinusitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Chronic tonsillitis 0 0			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	5 / 129 (3.88%)	1 / 128 (0.78%)	6 / 128 (4.69%)
occurrences (all)	5	1	7
Cystitis			
subjects affected / exposed	3 / 129 (2.33%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	4	3	0
Device related infection			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Device related sepsis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Diverticulitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	4 / 129 (3.10%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	5	1	0
Enteritis infectious			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Erysipelas			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Eye infection			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Gastric infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
subjects affected / exposed	4 / 129 (3.10%)	1 / 128 (0.78%)	3 / 128 (2.34%)
occurrences (all)	5	1	3
Gastroenteritis viral			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	4	0
Gastrointestinal candidiasis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Gastrointestinal infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal viral infection			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Genital infection female			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Gingivitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Groin abscess			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Helicobacter gastritis			

subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Helicobacter infection			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Hepatitis B			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Herpes simplex			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	1	8	2
Herpes virus infection			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Herpes zoster			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Incision site abscess			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	6 / 129 (4.65%)	8 / 128 (6.25%)	11 / 128 (8.59%)
occurrences (all)	7	12	16
Joint abscess			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	2 / 128 (1.56%)
occurrences (all)	0	2	2
Localised infection			

subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	0	1	2
Lower respiratory tract infection			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	19 / 129 (14.73%)	16 / 128 (12.50%)	19 / 128 (14.84%)
occurrences (all)	44	34	40
Oesophageal candidiasis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Onychomycosis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Oral candidiasis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	2 / 128 (1.56%)
occurrences (all)	1	0	4
Oral fungal infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Otitis media			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Otitis media chronic			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Periodontitis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Pharyngitis			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	3 / 128 (2.34%)
occurrences (all)	1	0	4
Pharyngitis bacterial			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	5 / 129 (3.88%)	3 / 128 (2.34%)	5 / 128 (3.91%)
occurrences (all)	5	3	6
Pulpitis dental			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	1	1	1
Pyelonephritis chronic			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection			
subjects affected / exposed	5 / 129 (3.88%)	4 / 128 (3.13%)	6 / 128 (4.69%)
occurrences (all)	9	4	6
Respiratory tract infection viral			
subjects affected / exposed	4 / 129 (3.10%)	5 / 128 (3.91%)	8 / 128 (6.25%)
occurrences (all)	4	6	13
Rhinitis			
subjects affected / exposed	5 / 129 (3.88%)	5 / 128 (3.91%)	1 / 128 (0.78%)
occurrences (all)	5	8	1
Salpingo-oophoritis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	3 / 129 (2.33%)	3 / 128 (2.34%)	10 / 128 (7.81%)
occurrences (all)	7	6	16
Skin infection			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	1
Tinea pedis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Tongue fungal infection			

subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Tonsillitis			
subjects affected / exposed	1 / 129 (0.78%)	3 / 128 (2.34%)	1 / 128 (0.78%)
occurrences (all)	2	3	1
Tonsillitis bacterial			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Tooth abscess			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Tracheitis			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	4	0	1
Tracheobronchitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	16 / 129 (12.40%)	8 / 128 (6.25%)	13 / 128 (10.16%)
occurrences (all)	41	9	27
Urinary tract infection			
subjects affected / exposed	4 / 129 (3.10%)	1 / 128 (0.78%)	5 / 128 (3.91%)
occurrences (all)	4	2	5
Vaginal infection			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Varicella			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Viral infection			
subjects affected / exposed	4 / 129 (3.10%)	5 / 128 (3.91%)	3 / 128 (2.34%)
occurrences (all)	5	5	3
Viral rhinitis			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			

subjects affected / exposed	1 / 129 (0.78%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	1	2	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Calcium deficiency			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Decreased appetite			
subjects affected / exposed	2 / 129 (1.55%)	2 / 128 (1.56%)	2 / 128 (1.56%)
occurrences (all)	6	2	3
Dehydration			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Diabetes mellitus			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Fluid overload			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	2	0	1
Fluid retention			
subjects affected / exposed	2 / 129 (1.55%)	1 / 128 (0.78%)	2 / 128 (1.56%)
occurrences (all)	2	1	2
Glucose tolerance impaired			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	1	0	0
Gout			
subjects affected / exposed	2 / 129 (1.55%)	2 / 128 (1.56%)	1 / 128 (0.78%)
occurrences (all)	2	2	1
Hypercholesterolaemia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1

Hyperglycaemia			
subjects affected / exposed	1 / 129 (0.78%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	1	1	0
Hyperkalaemia			
subjects affected / exposed	2 / 129 (1.55%)	4 / 128 (3.13%)	0 / 128 (0.00%)
occurrences (all)	2	4	0
Hyperlipidaemia			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Hypernatraemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	3 / 129 (2.33%)	1 / 128 (0.78%)	3 / 128 (2.34%)
occurrences (all)	3	1	3
Hypocalcaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	10 / 129 (7.75%)	6 / 128 (4.69%)	5 / 128 (3.91%)
occurrences (all)	12	9	7
Hypomagnesaemia			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	1 / 128 (0.78%)
occurrences (all)	0	1	2
Hyponatraemia			
subjects affected / exposed	1 / 129 (0.78%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	1	0	1
Impaired fasting glucose			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Insulin resistance			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1

Iron deficiency			
subjects affected / exposed	0 / 129 (0.00%)	3 / 128 (2.34%)	2 / 128 (1.56%)
occurrences (all)	0	3	2
Mineral metabolism disorder			
subjects affected / exposed	0 / 129 (0.00%)	0 / 128 (0.00%)	1 / 128 (0.78%)
occurrences (all)	0	0	1
Obesity			
subjects affected / exposed	0 / 129 (0.00%)	2 / 128 (1.56%)	0 / 128 (0.00%)
occurrences (all)	0	2	0
Steroid diabetes			
subjects affected / exposed	2 / 129 (1.55%)	0 / 128 (0.00%)	0 / 128 (0.00%)
occurrences (all)	2	0	0
Vitamin D deficiency			
subjects affected / exposed	0 / 129 (0.00%)	1 / 128 (0.78%)	0 / 128 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 November 2014	Permit short term phosphodiesterase type 5 inhibitor (PDE5I) use prior to enrollment. Allow temporary discontinuation (up to 14 days) of study treatment to permit temporary treatment with prohibited medications for comorbidities. Addition of riociguat as a prohibited medication.
28 August 2020	To increase, in a blinded manner, the dose for subjects receiving 5 mg (TID) to 20 mg (TID), the approved dose in these 5 countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study stopped by DMC after first IA (primary objective met). OS and clinical worsening (CW) sig level adjusted for IA (99.7% CIs used instead of 95% CIs). OS 80mg v 5mg primary, CW 80mg v 5mg key secondary. Other comparisons / endpoints are nominal.

Notes: