Clinical trial results:
A Randomised Phase II/III trial of peri-operative Chemotherapy with or without Bevacizumab in Operable Oesophagogastric Adenocarcinoma and A Feasibility Study Evaluating Lapatinib in HER-2 Positive Oesophagogastric Adenocarcinoma and (in selected centres) MRI and FDG-PET/CT Sub-studies

Summary

EudraCT number	2006-000811-12
Trial protocol	GB DE
Global end of trial date	30 November 2018

Results information

Result version number	v1 (current)
This version publication date	29 August 2020
First version publication date	29 August 2020

Trial information

Trial identification

Sponsor protocol code	ST03

Additional study identifiers

ISRCTN number	ISRCTN46020948
ClinicalTrials.gov id (NCT number)	NCT00450203
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Research Council
Sponsor organisation address	90 High Holborn, London, United Kingdom, WC1V 6LJ
Public contact	ST03 Trial Manager, Medical Research Council Clinical Trials Unit, +44 02076704801, mrcctu.st03@ucl.ac.uk
Scientific contact	ST03 Trial Manager, Medical Research Council Clinical Trials Unit, +44 02076704801, mrcctu.st03@ucl.ac.uk

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	10 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 April 2017
Global end of trial reached?	Yes
Global end of trial date	30 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess safety and overall survival of patients by adding the monoclonal antibody bevacizumab to Epirubicin, Cisplatin, Capecitabine (ECX) chemotherapy administered peri-operatively in patients with operable oesophagogastric adenocarcinoma and (in selected centres) a feasibility study evaluating the safety and feasibility of adding lapatinib, a small molecule tyrosine kinase inhibitor of HER-2 and epidermal growth factor receptor to peri-operative ECX chemotherapy in patients with HER-2 positive tumours.

Protection of trial subjects:

Patients provided informed consent prior to entering the trial. All patients were followed and treated by qualified clinicians in specialised teams.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 2007
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	United Kingdom: 1109
Worldwide total number of subjects	1109
EEA total number of subjects	1109

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)	617
From 65 to 84 years	492

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients recruited between 31st October 2007 and 21st April 2016.

Pre-assignment

Screening details:

Patients were screened for eligibility by centres, but information on numbers were not recorded.

From 25th February 2013, patients underwent HER2 testing prior to randomisation, to assess eligibility for the feasibility study. 441 patients were assessed during this period, 46 of whom were subsequently randomised into that part of the study.

Period 1

Period 1 title	Main trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	ECX (Arm A)

Arm description:

Epirubicin, cisplatin, capecitabine.
Control arm for Bevacizumab comparison.

Arm type	Active comparator
Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg/m2 given on day 1 on 21-day chemo cycle. Three cycles pre- and post-operatively.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

60mg/m2 given on day 1 on 21-day chemo cycle. Three cycles pre- and post-operatively.

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

Dosage and administration details:

1250mg/m2 taken orally on each day of 21-day cycle. Three cycles pre- and post-operatively.

Arm title	ECX + Bev (arm B)

Arm description:

Epirubicin, cisplatin, capecitabine, plus Bevacizumab.
Experimental arm for Bev comparison.

Arm type	Experimental

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg/m2 given on day 1 on 21-day chemo cycle. Three cycles pre- and post-operatively.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

7.5mg/kg on day 1 of each 21-day chemotherapy cycle. Three cycles pre- and post-operatively alongside other chemotherapy agents. Patients received a further six doses, once every 21 days, as maintenance treatment after post-operative chemotherapy.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

60mg/m2 given on day 1 on 21-day chemo cycle. Three cycles pre- and post-operatively.

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

Dosage and administration details:

1250mg/m2 taken orally on each day of 21-day cycle. Three cycles pre- and post-operatively.

Arm title	ECX (Arm C)

Arm description:

Epirubicin, cisplatin, capecitabine.
Control arm for the Lapatinib comparison. HER2 positive patients.

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1250mg/m2 taken orally on each day of 21-day cycle. Three cycles pre- and post-operatively.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg/m2 given on day 1 on 21-day chemo cycle. Three cycles pre- and post-operatively.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

60mg/m2 given on day 1 on 21-day chemo cycle. Three cycles pre- and post-operatively.

Arm title	ECX + Lap (Arm D)

Arm description:

Epirubicin, cisplatin, capecitabine.
Experimental arm for the Lapatinib comparison. HER2 positive patients.

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

Dosage and administration details:

1000mg/m2 taken orally on each day of 21-day cycle. Three cycles pre- and post-operatively.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

50mg/m2 given on day 1 on 21-day chemo cycle. Three cycles pre- and post-operatively.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

60mg/m2 given on day 1 on 21-day chemo cycle. Three cycles pre- and post-operatively.

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

Dosage and administration details:

1250mg taken orally on each day of 21-day chemotherapy cycle. Three pre- and post-operative cycles alongside other chemotherapy agents. Patients further received a maintenance dose of 1500mg, taken daily for six 21-day cycles, following post-op chemotherapy.

Number of subjects in period 1	ECX (Arm A)	ECX + Bev (arm B)	ECX (Arm C)
Started	533	530	24
Completed	522	512	24
Not completed	11	18	0
Withdrew consent prior to surgery	11	18	-

Number of subjects in period 1	ECX + Lap (Arm D)
Started	22
Completed	20
Not completed	2
Withdrew consent prior to surgery	2

Baseline characteristics

Reporting groups	
Reporting group title	ECX (Arm A)
Reporting group description:	
Epirubicin, cisplatin, capecitabine. Control arm for Bevacizumab comparison.	
Reporting group title	ECX + Bev (arm B)
Reporting group description:	
Epirubicin, cisplatin, capecitabine, plus Bevacizumab. Experimental arm for Bev comparison.	
Reporting group title	ECX (Arm C)
Reporting group description:	
Epirubicin, cisplatin, capecitabine. Control arm for the Lapatinib comparison. HER2 positive patients.	
Reporting group title	ECX + Lap (Arm D)
Reporting group description:	
Epirubicin, cisplatin, capecitabine. Experimental arm for the Lapatinib comparison. HER2 positive patients.	

Reporting group values	ECX (Arm A)	ECX + Bev (arm B)	ECX (Arm C)
Number of subjects	533	530	24
Age categorical			
Age at date of randomisation			
Units: Subjects			
Adults (18-64 years)	304	289	12
From 65-84 years	229	241	12
Age continuous			
Age at date of randomisation			
Units: years			
median	63	64	64
inter-quartile range (Q1-Q3)	56 to 68	56 to 69	57 to 68
Gender categorical Units: Subjects			
Female	425	434	21
Male	108	96	3
WHO performance status Units: Subjects			
Normal activity	381	376	17
Restricted in physical activity	152	154	7
Site of tumour Units: Subjects			
Stomach	194	189	4
OGJ (Type II)	105	95	4
OGJ (Type III)	98	109	4
OGJ (Type I)	62	67	4
Lower oesophageal	74	70	8

Reporting group values	ECX + Lap (Arm D)	Total	
Number of subjects	22	1109	

Age categorical			
Age at date of randomisation			
Units: Subjects			
Adults (18-64 years)	12	617	
From 65-84 years	10	492	
Age continuous			
Age at date of randomisation			
Units: years			
median	62		
inter-quartile range (Q1-Q3)	54 to 71	-	
Gender categorical			
Units: Subjects			
Female	14	894	
Male	8	215	
WHO performance status			
Units: Subjects			
Normal activity	14	788	
Restricted in physical activity	8	321	
Site of tumour			
Units: Subjects			
Stomach	4	391	
OGJ (Type II)	4	208	
OGJ (Type III)	2	213	
OGJ (Type I)	5	138	
Lower oesophageal	7	159	

End points

End points reporting groups

Reporting group title	ECX (Arm A)
Reporting group description:	
Epirubicin, cisplatin, capecitabine. Control arm for Bevacizumab comparison.	
Reporting group title	ECX + Bev (arm B)
Reporting group description:	
Epirubicin, cisplatin, capecitabine, plus Bevacizumab. Experimental arm for Bev comparison.	
Reporting group title	ECX (Arm C)
Reporting group description:	
Epirubicin, cisplatin, capecitabine. Control arm for the Lapatinib comparison. HER2 positive patients.	
Reporting group title	ECX + Lap (Arm D)
Reporting group description:	
Epirubicin, cisplatin, capecitabine. Experimental arm for the Lapatinib comparison. HER2 positive patients.	

Primary: Overall survival at 3 years (Bev comparison)

End point title	Overall survival at 3 years (Bev comparison)[1]
End point description:	
End point type	Primary
End point timeframe:	
Overall survival rate at 3 years post-randomisation	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only applies to the Bavacizumab comparison, involving only arms A and B.

End point values	ECX (Arm A)	ECX + Bev (arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	530		
Units: Percentage survival				
number (confidence interval 95%)	50.3 (45.5 to 54.9)	48.1 (43.2 to 52.7)		

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	ECX (Arm A) v ECX + Bev (arm B)

Number of subjects included in analysis	1063
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.29

Primary: Rate of preoperative diarrhoea (Lapatinib comparison)

End point title	Rate of preoperative diarrhoea (Lapatinib comparison)[2][3]

End point description:

Number (percentage) of patients experiencing grade 3/4 diarrhoea pre-operatively.

End point type	Primary

End point timeframe:

Events from randomisation until surgery.

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to early termination of the trial, no formal statistical analyses were conducted.

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pre-operative diarrhoea was an outcome measure for the Lapatinib feasibility aspect of the trial, and only involves arms C and D.

End point values	ECX (Arm C)	ECX + Lap (Arm D)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	20		
Units: Patients				
Grade 3/4 diarrhoea	0	4		
No grade 3/4 diarrhoea	24	15		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (Bev comparison)

End point title	Progression free survival (Bev comparison)[4]

End point description:

PFS calculated from randomisation until first occurremce of disease recurrence or death. Censored at date of last follow-up.

End point type	Secondary

End point timeframe:

Progression free survival at 3 years post-randomisation

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only applies to the Bavacizumab comparison, involving only arms A and B.

End point values	ECX (Arm A)	ECX + Bev (arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	530		
Units: Percentage				
number (confidence interval 95%)	0.43 (0.39 to 0.48)	0.41 (0.36 to 0.46)		

Statistical analyses

Statistical analysis title	Progression free survival
Comparison groups	ECX (Arm A) v ECX + Bev (arm B)
Number of subjects included in analysis	1063
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.23

Secondary: Disease free survival (Bev comparison)

End point title	Disease free survival (Bev comparison)[5]

End point description:

DFS measured from a landmark point of 6 months post-randomisation, to allow for any differences in timing of surgery, to the first occurrence of disease recurrence or death. Patients who had an event before the landmark point and those who had a macroscopically imcomplete (R2) resection or no resection were deemed to have had a DFS event at time zero. Censored at date of last follow-up.

End point type	Secondary

End point timeframe:

DFS from 6 months post-randomisation.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only applies to the Bavacizumab comparison, involving only arms A and B.

End point values	ECX (Arm A)	ECX + Bev (arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	530		
Units: Percent				
number (confidence interval 95%)	0.40 (0.35 to 0.44)	0.38 (0.33 to 0.43)		

Statistical analyses

Statistical analysis title	Disease free survival
Comparison groups	ECX (Arm A) v ECX + Bev (arm B)
Number of subjects included in analysis	1063
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.62
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.22

Secondary: Response to chemotherapy (Bev comparison)

End point title	Response to chemotherapy (Bev comparison)[6]

End point description:

RECIST response to pre-operative chemotherapy. Response is a partial or complete response. Patients with stable disease, progressive disease, or who had died before the RECIST assessment were regarded as non-responders.

End point type	Secondary

End point timeframe:

Response to chemotherapy assessed at surgery

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only applies to the Bavacizumab comparison, involving only arms A and B.

End point values	ECX (Arm A)	ECX + Bev (arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	438	437		
Units: Patients				
Response	183	177		
Non-response	255	260		

Statistical analyses

Statistical analysis title	Response to chemotherapy
Comparison groups	ECX (Arm A) v ECX + Bev (arm B)
Number of subjects included in analysis	875
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Chi-squared

Secondary: R0 resection rate (Bev comparison)

End point title	R0 resection rate (Bev comparison)[7]

End point description:

Proportion of patients undergoing R0 resection

End point type	Secondary

End point timeframe:

Resection status assessed at surgery.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This outcome measure only applies to the Bavacizumab comparison, involving only arms A and B.

End point values	ECX (Arm A)	ECX + Bev (arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	505	497		
Units: Patients				
R0	321	305		
R1+	184	192		

Statistical analyses

Statistical analysis title	R0 resection rate
Comparison groups	ECX (Arm A) v ECX + Bev (arm B)

Number of subjects included in analysis	1002
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.47
Method	Chi-squared

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: At any time following randomisation	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	ECX (Arm A)
Reporting group description: Epirubicin, cisplatin, capecitabine. Control arm for Bevacizumab comparison.	
Reporting group title	ECX + Bev (arm B)
Reporting group description: Epirubicin, cisplatin, capecitabine, plus Bevacizumab. Experimental arm for Bev comparison.	
Reporting group title	ECX (Arm C)
Reporting group description: Epirubicin, cisplatin, capecitabine. Control arm for the Lapatinib comparison. HER2 positive patients.	
Reporting group title	ECX + Lap (Arm D)
Reporting group description: Epirubicin, cisplatin, capecitabine. Experimental arm for the Lapatinib comparison. HER2 positive patients.	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Only serious adverse events were collected.

Serious adverse events	ECX (Arm A)	ECX + Bev (arm B)	ECX (Arm C)
Total subjects affected by serious adverse events			
subjects affected / exposed	411 / 533 (77.11%)	511 / 530 (96.42%)	16 / 24 (66.67%)
number of deaths (all causes)	301	308	12
number of deaths resulting from adverse events			
Vascular disorders			
Anastomotic haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Aortic thrombosis			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Arterial thrombosis			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (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
Central nervous system haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Cerebrovascular accident			
subjects affected / exposed	2 / 533 (0.38%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Deep vein thrombosis			
subjects affected / exposed	3 / 533 (0.56%)	7 / 530 (1.32%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	3 / 3	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	3 / 533 (0.56%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Exsanguination			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Gastric haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (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
Gastrointestinal haemorrhage			

subjects affected / exposed	3 / 533 (0.56%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	2 / 533 (0.38%)	4 / 530 (0.75%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Hypertension			
subjects affected / exposed	0 / 533 (0.00%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal infarction			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Intestinal ischaemia			
subjects affected / exposed	1 / 533 (0.19%)	4 / 530 (0.75%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	3 / 533 (0.56%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phlebitis			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Post procedural haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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 embolism			
subjects affected / exposed	39 / 533 (7.32%)	38 / 530 (7.17%)	3 / 24 (12.50%)
occurrences causally related to treatment / all	34 / 39	31 / 38	2 / 3
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Renal vein thrombosis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subclavian vein thrombosis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 533 (0.38%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	4 / 533 (0.75%)	11 / 530 (2.08%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	2 / 4	9 / 11	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular pain			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Surgical and medical procedures			
Coronary arterial stent insertion			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Oesophageal anastomosis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	10 / 533 (1.88%)	11 / 530 (2.08%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	4 / 11	4 / 11	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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 / 533 (0.38%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 3	0 / 0
Decreased appetite			
subjects affected / exposed	4 / 533 (0.75%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extravasation			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Fatigue			
subjects affected / exposed	2 / 533 (0.38%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			

subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Hypothermia			
subjects affected / exposed	0 / 533 (0.00%)	0 / 530 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	3 / 533 (0.56%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lethargy			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 533 (0.38%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	1 / 2	1 / 2	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	2 / 533 (0.38%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Peripheral swelling			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Pyrexia			
subjects affected / exposed	2 / 533 (0.38%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 2	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Hypersensitivity			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Aspiration			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Bronchial fistula			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Chest pain			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Dyspnoea			
subjects affected / exposed	4 / 533 (0.75%)	5 / 530 (0.94%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 5	2 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Pleural effusion			
subjects affected / exposed	2 / 533 (0.38%)	1 / 530 (0.19%)	0 / 24 (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
Pleuritic pain			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Pneumonia aspiration			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Pneumothorax			

subjects affected / exposed	3 / 533 (0.56%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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 distress			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Blood creatinine increased			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			

subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Drain site complication			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Oesophageal injury			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Post procedural complication			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (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
Procedural complication			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Procedural haemorrhage			
subjects affected / exposed	2 / 533 (0.38%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			

subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Wound complication			
subjects affected / exposed	4 / 533 (0.75%)	4 / 530 (0.75%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 4	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	3 / 533 (0.56%)	0 / 530 (0.00%)	0 / 24 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	2 / 533 (0.38%)	0 / 530 (0.00%)	0 / 24 (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
Arrhythmia supraventricular			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Atrial fibrillation			
subjects affected / exposed	7 / 533 (1.31%)	3 / 530 (0.57%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	2 / 7	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	2 / 533 (0.38%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 3	0 / 0
Cardiac disorder			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Chest pain			
subjects affected / exposed	4 / 533 (0.75%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 4	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Coronary artery dissection			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Coronary artery thrombosis			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dizziness			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Dyspnoea			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Myocardial infarction			
subjects affected / exposed	2 / 533 (0.38%)	5 / 530 (0.94%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	4 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Sinus tachycardia			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (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
Syncope			

subjects affected / exposed	3 / 533 (0.56%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	2 / 533 (0.38%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 533 (0.19%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dystonia			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Facial paralysis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Headache			

subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukoencephalopathy			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Loss of consciousness			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (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
Syncope			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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	3 / 533 (0.56%)	5 / 530 (0.94%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphatic duct injury			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Lymphatic fistula			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Neutropenia			
subjects affected / exposed	1 / 533 (0.19%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Thrombocytopenia			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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			
Abdominal adhesions			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Abdominal pain			

subjects affected / exposed	10 / 533 (1.88%)	14 / 530 (2.64%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	3 / 11	9 / 14	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anal fistula			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Aortoenteric fistula			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Constipation			
subjects affected / exposed	6 / 533 (1.13%)	6 / 530 (1.13%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	3 / 6	3 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diaphragmatic hernia			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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			
subjects affected / exposed	9 / 533 (1.69%)	9 / 530 (1.70%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	9 / 9	8 / 9	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Dyspepsia			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Dysphagia			
subjects affected / exposed	12 / 533 (2.25%)	14 / 530 (2.64%)	2 / 24 (8.33%)
occurrences causally related to treatment / all	2 / 14	3 / 17	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Enterocutaneous fistula			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (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
Gastric haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric perforation			
subjects affected / exposed	2 / 533 (0.38%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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 anastomotic leak			
subjects affected / exposed	30 / 533 (5.63%)	62 / 530 (11.70%)	2 / 24 (8.33%)
occurrences causally related to treatment / all	2 / 30	27 / 63	0 / 2
deaths causally related to treatment / all	0 / 2	4 / 5	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	2 / 533 (0.38%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal fistula			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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 haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Gastrointestinal pain			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (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
Gastrointestinal perforation			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	3 / 533 (0.56%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 3	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			

subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Hiatus hernia			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Ileus			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Intestinal ischaemia			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Intestinal obstruction			
subjects affected / exposed	3 / 533 (0.56%)	4 / 530 (0.75%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (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
Nausea			
subjects affected / exposed	4 / 533 (0.75%)	4 / 530 (0.75%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	3 / 4	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			

subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (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
Odynophagia			
subjects affected / exposed	2 / 533 (0.38%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal fistula			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oesophageal obstruction			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Oesophageal perforation			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Oesophageal stenosis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Oesophagitis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Pyloric stenosis			

subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Rectal haemorrhage			
subjects affected / exposed	2 / 533 (0.38%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	3 / 533 (0.56%)	0 / 530 (0.00%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	3 / 533 (0.56%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheo-oesophageal fistula			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	5 / 533 (0.94%)	10 / 530 (1.89%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	3 / 5	4 / 10	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary tract disorder			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Cholecystitis			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Jaundice			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 533 (0.38%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin wound			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Prerenal failure			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Renal failure			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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

Ureterolithiasis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Urinary retention			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Hypoglycaemia			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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			
Ankle fracture			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Arthralgia			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Arthritis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Gout			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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

Gouty arthritis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Muscular weakness			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Tendonitis			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Upper limb fracture			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	2 / 533 (0.38%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	2 / 533 (0.38%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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
Enterocolitis infectious			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Infection			
subjects affected / exposed	11 / 533 (2.06%)	17 / 530 (3.21%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	11 / 12	10 / 19	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	16 / 533 (3.00%)	10 / 530 (1.89%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	3 / 16	5 / 10	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	28 / 533 (5.25%)	26 / 530 (4.91%)	1 / 24 (4.17%)
occurrences causally related to treatment / all	27 / 28	27 / 27	1 / 1
deaths causally related to treatment / all	3 / 3	4 / 4	0 / 0
Pleural infection			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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 / 533 (1.31%)	10 / 530 (1.89%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 7	3 / 10	0 / 0
deaths causally related to treatment / all	0 / 1	1 / 1	0 / 0
Post procedural infection			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural pneumonia			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (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
Respiratory tract infection			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 533 (0.56%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Tonsillitis			

subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Urinary tract infection			
subjects affected / exposed	3 / 533 (0.56%)	3 / 530 (0.57%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Wound infection			
subjects affected / exposed	14 / 533 (2.63%)	10 / 530 (1.89%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 14	5 / 11	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Abnormal loss of weight			
subjects affected / exposed	1 / 533 (0.19%)	1 / 530 (0.19%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (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	7 / 533 (1.31%)	8 / 530 (1.51%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	6 / 7	8 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 533 (0.19%)	2 / 530 (0.38%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	0 / 533 (0.00%)	1 / 530 (0.19%)	0 / 24 (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
Hyponatraemia			
subjects affected / exposed	0 / 533 (0.00%)	2 / 530 (0.38%)	0 / 24 (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
Metabolic acidosis			
subjects affected / exposed	1 / 533 (0.19%)	0 / 530 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Serious adverse events	ECX + Lap (Arm D)		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events			
Vascular disorders			
Anastomotic haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic aneurysm			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aortic thrombosis			

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arterial thrombosis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Central nervous system haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Embolism				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Exsanguination				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypertension				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal infarction				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intra-abdominal haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral ischaemia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Phlebitis				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal vein thrombosis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Subclavian vein thrombosis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular pain				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Coronary arterial stent insertion				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal anastomosis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Complication associated with device				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Extravasation				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Flank pain				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypothermia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impaired healing				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lethargy				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malaise				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypersensitivity			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspiration			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchial fistula			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardio-respiratory arrest			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Chest pain			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epistaxis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleuritic pain			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory distress				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Delirium				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoglobin decreased				

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anastomotic leak			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drain site complication			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal injury			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural complication			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural complication			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Procedural pain			

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound complication				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound dehiscence				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia supraventricular				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorder				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery dissection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery thrombosis				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus tachycardia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				

subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dystonia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Facial paralysis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukoencephalopathy				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Loss of consciousness				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Orthostatic hypotension				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral motor neuropathy				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphatic duct injury			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lymphatic fistula			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortoenteric fistula				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diaphragmatic hernia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	4 / 22 (18.18%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Diarrhoea haemorrhagic				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Enteritis infectious				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Enterocutaneous fistula				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric perforation				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				

subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal anastomotic leak				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal fistula				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal pain				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal perforation				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematemesis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hiatus hernia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal ischaemia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Melaena				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction gastric				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Odynophagia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal fistula				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal obstruction				
subjects affected / exposed	2 / 22 (9.09%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Oesophageal perforation				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophageal stenosis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyloric stenosis				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tracheo-oesophageal fistula				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Biliary tract disorder				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Jaundice			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin wound			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prerenal failure			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Ureterolithiasis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Hyperglycaemia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypoglycaemia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Ankle fracture				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gout				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Gouty arthritis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain in extremity				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendonitis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper limb fracture				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal sepsis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal wall abscess				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile colitis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea infectious			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Empyema			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enteritis infectious			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis infectious			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 22 (4.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural infection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural infection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post procedural pneumonia				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tonsillitis				

subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Varicella				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Wound infection				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Abnormal loss of weight				
subjects affected / exposed	1 / 22 (4.55%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Decreased appetite				
subjects affected / exposed	0 / 22 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				

subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolic acidosis			
subjects affected / exposed	0 / 22 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ECX (Arm A)	ECX + Bev (arm B)	ECX (Arm C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 533 (0.00%)	0 / 530 (0.00%)	0 / 24 (0.00%)

Non-serious adverse events	ECX + Lap (Arm D)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2008	Version 2 of protocol. The main changes concerned the additional of the Translation sub study, additional funding available as well as further clarification to the protocol Patient Inclusion Criteria has been updated Patient Exclusion Criteria: patients with clinically apparent hearing impairment has been removed from the exclusion criteria. Warfarin has been removed as an excluded concomitant medication, but is advised that it should be used with caution. Guidance is given for patients with raised BP and hearing impairment. Tissue and Blood Collection for Translational Research has been added Capecitabine Diary Card has been added Cisplatin and Capecitabine dose modifications for ECX has been updated to be more reader friendly. If cisplatin is substituted for carboplatin, patients should continue to receive epirubicin. Instructions on all patients receiving lansoprazole 30mg od po, or an alternative proton pump inhibitor (PPI), is given. New guidance has been added for patients that remain unfit to commence post-operative chemotherapy, 10 weeks post surgery The intervals for the initial follow-up assessments have been corrected, this is also reflected in the ST03 Trial schema diagram and trial summary Specific toxicities requiring discontinuation of bevacizumab. Patients with any grade of fistulae should have bevacizumab discontinued Recommendations for managing patients that develop fistula are given. All grades of fistulae has been added as an ST03 notable event Sites will receive additional funding via per patient payments for the first 100 patients randomised The central pathology review has been updated and new information has been added to describe the collection of blood and tumour samples for future translational research Patient Information Sheet has been updated ST03 Trial Consent Form has been updated Trans ST03 Consent Form has been added
17 June 2009	Version 3 of protocol. The main changes concern the additional of the Type II junctional tumours to the inclusion criteria as well as further clarification to the protocol. Full details of the protocol changes are given in the summary of amendments to Version 3, however, the key changes include: Type II tumours now eligible for the trial 24 hour urine collection is no longer mandatory at baseline Patients with high frequency hearing loss are eligible for ST03, they should be treated with cisplatin but changed to carboplatin if there is any evidence of deterioration Patients with severe tinnitus should not be randomised Positive serology for HIV, Hepatitis C of active Hepatitis B have been added as exclusion criteria Some flexibility with screening assessments and investigations have been added Updated information on proteinuria to include use of urine protein-creatinine ratio New guidelines provided to include surgical techniques for Type II junctional tumours and information on performing totally minimally invasive surgery New table added to show CRF completion schedule for patients who do not complete protocol treatment Further guidance and clarification on various elements of the central pathology review and storage of translational ST03 samples SPC updated where necessary

01 February 2010	Protocol version 3 - Addendum 1 urgent safety amendment. A nadir blood count is now required during cycle 1 at approximately day 10 of treatment. Any patients who experience Grade 4 neutropenia should receive GCSF for 3-5 days starting on day 10. Any patients who have Grade 3 neutropenia should be treated with GCSF at the discretion of the Investigator. These patients should also receive GSCF during all further cycles of ECX+/-B.
27 May 2010	Version 4 of protocol The main changes concern the addition of a nadir blood count during cycle one and guidance for commencing GCSF, changes to the cardiac monitoring recommendations and TNM7 staging clarification. Section 6.1 Patient Inclusion Criteria Guidance for any patients staged according to the TNM7 staging criteria Cardiac function measured by MUGA can be above centre's LLN if this is lower than 50% Patients who have received chemotherapy or radiotherapy for a previous malignancy are ineligible Section 8.1 Treatment of Patients A nadir blood count is now required during cycle 1 at approximately day 10 of treatment and any patients who experience Grade 4 should receive GCSF for 3-5 days starting on day 10. Any patients who have Grade 3 neutropenia should be treated with GCSF at the discretion of the Investigator. These patients should also receive GSCF during all further cycles of ECX+/-B. Section 8.1.2 Cardiac Monitoring Patients in whom a drop in LVEF of >15% or to less than 50% is seen should have a further measurement taken 3 months later Section 8.4.2 Guidance on omitting doses of Bevacizumab Bevacizumab may be reintroduced if it was ceased following a reduction in LVEF if recovery to the normal range is observed at the next cardiac monitoring scan. Section 9.2.6 Hypertension An ACE inhibitor should be used as first line to treat hypertension. Section 11.2 Management of LVEF Where a range is reported, management should be based on the lower bound of the range. Any patients with a reduction in LVEF of >15% or to <50% should have an additional scan 3 months after the abnormal measurement. Epirubicin and/or Bevacizumab may be restarted if the LVEF recovers to >50%.
15 February 2011	Version 5 of protocol The main changes concern the inclusion of lower oesophageal and Type I tumours and associated updated staging, screening, surgery and pathology guidance, changes to the hypertension recommendations and ECG requirements, guidance on treatment recommendations for patients with symptomatic Pulmonary Embolisms and addition of the MRI Sub-study.
04 July 2011	Protocol version 5 - Addendum 1, urgent safety amendment The additional cardiac monitoring assessments (pre-op and post chemo ECHO/MUGAs) have been discontinued from the sECX+/- bevacizumab arms (Arms A and B) of the study following a safety analysis. Study visit schedules and CRF return schedules have also been updated to reflect this.

28 September 2012	Version 6 of protocol The main changes concern the addition of a lapatinib feasibility study within the ST03 trial. Selected centres will participate in this feasibility trial which will involve testing the HER-2 status of the patient's tumour biopsy centrally at the Royal Marsden Hospital (or locally if permitted) prior to randomisation into the trial. Patients with HER-2 positive tumours will be randomised to sECX Vs mECX+Lapatinib and patients with HER-2 negative or unknown/undefined tumours will be randomised to sECX+/-Bevacizumab. This is in response to newly published data in the advanced setting (73). Section B has been added to the protocol to include instructions for the selected centres involved in the feasibility study. Section A provides information for centres not involved in the feasibility study and the patients with HER-2 negative or unknown/undefined tumours randomised into the sECX+/-Bevacizumab arms. Section B provides information for the centres involved in the feasibility study on the registration of patients and the HER-2 sample testing process and then goes on to provide details for the management of patients with HER-2 positive tumours randomised to the sECX Vs mECX+Lapatinib arms.
01 October 2013	Protocol version 6 - addendum 1, urgent safety amendment Inclusion criteria for the ST03 main trial (sECX+/-bevacizumab comparison) amended to exclude patients with lower oesophageal, Siewert Type I, II or III oesophagogastric junctional (OGJ) adenocarcinomas from entering this comparison. The trial remains open and unchanged for patients with gastric adenocarcinomas who do not require oesophagogastrectomy. Patients with lower oesophageal, Siewert Type I, II or III OGJ adenocarcinomas who have already entered the sECX+B arm (Arm B) must not receive any further pre-operative bevacizumab. Following surgery patients may resume treatment with bevacizumab provided that there are no other contraindications.
17 February 2014	Version 7 of protocol The main changes to the protocol are organisational and have been made to reflect the closure of the bevacizumab comparison and to allow patients with a negative or unknown/undefined HER-2 status to be registered into the observation only, imaging sub-studies (MRI and PET/CT) at participating centres.
25 June 2015	Protocol version 9 The changes mainly concern including patients scheduled to receive chemotherapy regimes other than ECX to register into the PET/CT and/or MRI Sub studies only. Patients entering one or both studies that are also randomised into the feasibility study should be scheduled to receive sECX or mECX+L as per allocated treatment.
19 October 2017	Protocol version 10. The changes made were mainly to reflect the current status of each of the 4 studies within the ST03 protocol.

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.

Only around half of patients start post-operative chemotherapy, and only one fifth completed all maintenance treatment.
Small sample size for lapatinib study (feasibility only). Regimens (chemo and HER2-targeted) used have since been superceded.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28163000

http://www.ncbi.nlm.nih.gov/pubmed/31219517