Clinical trial results:
An open-label, randomised, phase III Study cOmparing trifLuridine/tipiracil (S 95005) in combination with bevacizumab to capecitabine in combination with bevacizumab in firST-line treatment of patients with metastatIC colorectal cancer who are not candidatE for intensive therapy (SOLSTICE study)

Summary

EudraCT number	2017-004059-22
Trial protocol	GB IE SE AT ES DK LT NL LV SK CZ HU DE PL PT BG IT RO
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	26 May 2022
First version publication date	26 May 2022

Trial information

Trial identification

Sponsor protocol code	CL3-95005-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03869892
WHO universal trial number (UTN)	U1111-1206-3198

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier
Sponsor organisation address	50 rue Carnot, Suresnes, France, 92284
Public contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1.55.72.43.66, clinicaltrials@servier.com
Scientific contact	Clinical Studies Department, Institut de Recherches Internationales Servier, +33 1.55.72.43.66, clinicaltrials@servier.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	09 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 June 2021
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of S 95005 in combination with bevacizumab over capecitabine in combination with bevacizumab in terms of progression-free survival (PFS) based on Investigator assessment in first-line treatment of patients with unresectable metastatic colorectal cancer who are not candidate for intensive therapy.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki and applicable regulatory requirements. After the subject has ended his/her participation in the trial, the investigator provided appropriate medication and/or arranged access to appropriate care for the patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 2019
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	Netherlands: 21
Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Romania: 23
Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 83
Country: Number of subjects enrolled	Sweden: 10
Country: Number of subjects enrolled	United Kingdom: 53
Country: Number of subjects enrolled	Austria: 13
Country: Number of subjects enrolled	Bulgaria: 23
Country: Number of subjects enrolled	Czechia: 12
Country: Number of subjects enrolled	Denmark: 36
Country: Number of subjects enrolled	Estonia: 14
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Hungary: 74
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Latvia: 11
Country: Number of subjects enrolled	Lithuania: 14

Country: Number of subjects enrolled	Russian Federation: 126
Country: Number of subjects enrolled	Ukraine: 132
Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Brazil: 42
Country: Number of subjects enrolled	Australia: 15
Worldwide total number of subjects	856
EEA total number of subjects	473

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)	204
From 65 to 84 years	608
85 years and over	44

Subject disposition

Recruitment

Recruitment details:

Investigators were oncologists.

Pre-assignment

Screening details:

Male or female participant aged ≥ 18 years old with metastatic colorectal cancer (mCRC), RAS status determined on tumour biopsy, neither candidate for standard full dose combination chemotherapy with irinotecan or oxaliplatin nor for curative resection of metastatic lesions. No previous systemic anticancer therapy for unresectable mCRC.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	S95005 + bevacizumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	S95005
Investigational medicinal product code	
Other name	trifluridine/tipiracil
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

S95005 was administered orally twice a day (35 mg/m²/dose), within 1 hour after completion of morning and evening meals, Days 1 to 5 and Days 8 to 12, followed by a 14-day rest; with bevacizumab (5 mg/kg, intravenously) administered every 2 weeks (Day 1 and Day 15).

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously at 5 mg/kg at Day 1 and Day 15 of each cycle in combination with S95005.

Arm title	Capecitabine + bevacizumab

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine was administered orally twice daily (1250 mg/m²) on Days 1 to 14 of each cycle, with bevacizumab (7.5 mg/kg, IV) administered on Day 1 of each cycle. This treatment cycle was repeated every 3 weeks. The starting dose of capecitabine could be reduced to 1000mg/m² according to local clinical practice.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered intravenously at 7.5 mg/kg on Day 1 of each cycle in combination with capecitabine.

Number of subjects in period 1	S95005 + bevacizumab	Capecitabine + bevacizumab
Started	426	430
Completed	0	0
Not completed	426	430
Radiological progressive disease	168	165
Other, Medical reason	8	8
Clinical progressive disease	39	38
Radiological and clinical progressive disease	34	23
Continuing study on-treatment	74	59
Adverse event	71	101
Patient becoming resectable	2	3
Randomised but not enrolled or not treated	3	-
Randomised but not enrolled	-	3
Lost to follow-up	-	1
Non-medical reason	27	26
Protocol deviation	-	3

Baseline characteristics

Reporting groups	
Reporting group title	S95005 + bevacizumab
Reporting group description: -	
Reporting group title	Capecitabine + bevacizumab
Reporting group description: -	

Reporting group values	S95005 + bevacizumab	Capecitabine + bevacizumab	Total
Number of subjects	426	430	856
Age categorical Units: Subjects			
Adults (18-64 years)	97	107	204
From 65-84 years	309	299	608
85 years and over	20	24	44
Age continuous Units: years			
arithmetic mean	71.6	71.2	
standard deviation	± 10.0	± 10.8	-
Gender categorical Units: Subjects			
Female	186	204	390
Male	240	226	466

End points

End points reporting groups	
Reporting group title	S95005 + bevacizumab
Reporting group description: -	
Reporting group title	Capecitabine + bevacizumab
Reporting group description: -	

Primary: Progression Free Survival (PFS)	
End point title	Progression Free Survival (PFS)
End point description:	
Tumour assessments were performed by the investigator based on RECIST 1.1 at baseline then every 8 weeks until radiologic progression.	
End point type	Primary
End point timeframe:	
PFS was defined as the time from the date of randomisation until the date of radiologic disease progression or death due to any cause.	

End point values	S95005 + bevacizumab	Capecitabine + bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	426	430		
Units: Number of PFS events	309	320		

Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description:	
The primary analysis was conducted after reaching 628 PFS events.	
Comparison groups	S95005 + bevacizumab v Capecitabine + bevacizumab
Number of subjects included in analysis	856
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.02

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred or worsened or became serious between the first or bevacizumab intake and the last IMP intake + 35 days (both included).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	S95005 + bevacizumab
Reporting group description: -	
Reporting group title	Capecitabine + bevacizumab

Reporting group description: -

Serious adverse events	S95005 + bevacizumab	Capecitabine + bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	176 / 423 (41.61%)	197 / 427 (46.14%)	
number of deaths (all causes)	172	177	
number of deaths resulting from adverse events	5	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bronchial neoplasm			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibroma			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lentigo maligna			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	19 / 423 (4.49%)	32 / 427 (7.49%)	
occurrences causally related to treatment / all	0 / 20	0 / 32	
deaths causally related to treatment / all	0 / 14	0 / 23	
Metastases to bladder			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to ovary			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spinal cord			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to uterus			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recurrent cancer			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tumour necrosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	7 / 423 (1.65%)	15 / 427 (3.51%)	
occurrences causally related to treatment / all	4 / 7	11 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	4 / 423 (0.95%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	4 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 423 (0.71%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 423 (0.24%)	4 / 427 (0.94%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	2 / 423 (0.47%)	4 / 427 (0.94%)	
occurrences causally related to treatment / all	2 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	7 / 423 (1.65%)	6 / 427 (1.41%)	
occurrences causally related to treatment / all	0 / 7	3 / 7	
deaths causally related to treatment / all	0 / 2	0 / 2	
Generalised oedema			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Oedema peripheral			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 423 (1.42%)	4 / 427 (0.94%)	
occurrences causally related to treatment / all	3 / 6	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 423 (0.24%)	4 / 427 (0.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 4	
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Loss of personal independence in daily activities			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian vein thrombosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic haemorrhage			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchial haemorrhage			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 423 (0.24%)	3 / 427 (0.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopnoea			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery thrombosis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	10 / 423 (2.36%)	30 / 427 (7.03%)	
occurrences causally related to treatment / all	8 / 10	19 / 31	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pulmonary haemorrhage			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary infarction			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyphrenia			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	2 / 423 (0.47%)	5 / 427 (1.17%)	
occurrences causally related to treatment / all	1 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hallucination, visual			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hallucinations, mixed			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure decreased			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood urea increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Body temperature increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 423 (0.00%)	3 / 427 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoembryonic antigen increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia test positive			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fibrin D dimer increased			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma output increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory marker increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella test positive			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	2 / 423 (0.47%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein C increased			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine output decreased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count increased			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic stenosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to anastomose			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 423 (0.71%)	6 / 427 (1.41%)	
occurrences causally related to treatment / all	0 / 4	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomal hernia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 423 (0.47%)	5 / 427 (1.17%)	
occurrences causally related to treatment / all	0 / 2	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			

subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	4 / 423 (0.95%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	1 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block first degree			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	3 / 423 (0.71%)	3 / 427 (0.70%)	
occurrences causally related to treatment / all	2 / 3	2 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	4 / 423 (0.95%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Extrasystoles			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apraxia			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral atrophy			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral small vessel ischaemic disease			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ventricle dilatation			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drop attacks			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysgeusia			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemianaesthesia			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic seizure			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemic seizure			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cerebral infarction			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	3 / 423 (0.71%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Memory impairment			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	4 / 423 (0.95%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 423 (0.47%)	5 / 427 (1.17%)	
occurrences causally related to treatment / all	0 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular encephalopathy			

subjects affected / exposed	0 / 423 (0.00%)	3 / 427 (0.70%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Vertebral artery stenosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White matter lesion			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 423 (6.62%)	7 / 427 (1.64%)	
occurrences causally related to treatment / all	19 / 30	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	10 / 423 (2.36%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	10 / 11	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	3 / 423 (0.71%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myelosuppression			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenia			
subjects affected / exposed	12 / 423 (2.84%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	15 / 15	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Splenic vein thrombosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 423 (0.95%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein thrombosis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	5 / 423 (1.18%)	5 / 427 (1.17%)	
occurrences causally related to treatment / all	1 / 6	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ascites			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colitis			

subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 423 (0.24%)	3 / 427 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	11 / 423 (2.60%)	10 / 427 (2.34%)	
occurrences causally related to treatment / all	8 / 11	10 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dieulafoy's vascular malformation			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Duodenal obstruction			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 423 (0.00%)	3 / 427 (0.70%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faeces discoloured			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastric perforation			

subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic erosive gastritis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernial eventration			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal perforation			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 423 (0.71%)	5 / 427 (1.17%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Ileus paralytic			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	9 / 423 (2.13%)	6 / 427 (1.41%)	
occurrences causally related to treatment / all	0 / 9	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 3	
Intestinal perforation			
subjects affected / exposed	3 / 423 (0.71%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	2 / 423 (0.47%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal stenosis			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant gastrointestinal obstruction			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 423 (0.71%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising colitis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis haemorrhagic			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal obstruction			

subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal stenosis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	4 / 423 (0.95%)	5 / 427 (1.17%)	
occurrences causally related to treatment / all	0 / 5	3 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Volvulus			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus of small bowel			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	5 / 423 (1.18%)	4 / 427 (0.94%)	
occurrences causally related to treatment / all	1 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder fistula			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant biliary obstruction			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 423 (0.71%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder perforation			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal injury			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcapsular renal haematoma			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric dilatation			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypopituitarism			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fistula			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	3 / 423 (0.71%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			

subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asymptomatic COVID-19			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial diarrhoea			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial prostatitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colostomy infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	5 / 423 (1.18%)	4 / 427 (0.94%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	5 / 423 (1.18%)	8 / 427 (1.87%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site abscess			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perineal abscess			

subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	2 / 423 (0.47%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal abscess			
subjects affected / exposed	0 / 423 (0.00%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	5 / 423 (1.18%)	4 / 427 (0.94%)	
occurrences causally related to treatment / all	1 / 5	1 / 4	
deaths causally related to treatment / all	0 / 2	1 / 1	
Pneumonia			
subjects affected / exposed	9 / 423 (2.13%)	5 / 427 (1.17%)	
occurrences causally related to treatment / all	3 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia chlamydial			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Septic shock			
subjects affected / exposed	2 / 423 (0.47%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Small intestine gangrene			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Staphylococcal infection			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal endocarditis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract candidiasis			

subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 423 (0.24%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 423 (0.24%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 423 (0.47%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 423 (0.47%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	9 / 423 (2.13%)	14 / 427 (3.28%)	
occurrences causally related to treatment / all	4 / 9	9 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	2 / 423 (0.47%)	3 / 427 (0.70%)	
occurrences causally related to treatment / all	0 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 423 (0.47%)	2 / 427 (0.47%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 423 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	S95005 + bevacizumab	Capecitabine + bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	412 / 423 (97.40%)	402 / 427 (94.15%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	52 / 423 (12.29%)	73 / 427 (17.10%)	
occurrences (all)	69	96	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	27 / 423 (6.38%)	23 / 427 (5.39%)	
occurrences (all)	33	23	
Asthenia			

subjects affected / exposed	95 / 423 (22.46%)	73 / 427 (17.10%)	
occurrences (all)	149	104	
Fatigue			
subjects affected / exposed	100 / 423 (23.64%)	105 / 427 (24.59%)	
occurrences (all)	148	151	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	23 / 423 (5.44%)	24 / 427 (5.62%)	
occurrences (all)	28	27	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	25 / 423 (5.91%)	24 / 427 (5.62%)	
occurrences (all)	44	25	
Aspartate aminotransferase increased			
subjects affected / exposed	23 / 423 (5.44%)	29 / 427 (6.79%)	
occurrences (all)	34	33	
Blood bilirubin increased			
subjects affected / exposed	22 / 423 (5.20%)	47 / 427 (11.01%)	
occurrences (all)	35	87	
Neutrophil count decreased			
subjects affected / exposed	91 / 423 (21.51%)	9 / 427 (2.11%)	
occurrences (all)	359	11	
Platelet count decreased			
subjects affected / exposed	38 / 423 (8.98%)	12 / 427 (2.81%)	
occurrences (all)	88	20	
Weight decreased			
subjects affected / exposed	47 / 423 (11.11%)	40 / 427 (9.37%)	
occurrences (all)	50	42	
White blood cell count decreased			
subjects affected / exposed	23 / 423 (5.44%)	2 / 427 (0.47%)	
occurrences (all)	73	3	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	2 / 423 (0.47%)	35 / 427 (8.20%)	
occurrences (all)	2	40	

Nervous system disorders			
Dysgeusia			
subjects affected / exposed	22 / 423 (5.20%)	13 / 427 (3.04%)	
occurrences (all)	39	28	
Headache			
subjects affected / exposed	23 / 423 (5.44%)	21 / 427 (4.92%)	
occurrences (all)	41	21	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	171 / 423 (40.43%)	54 / 427 (12.65%)	
occurrences (all)	321	71	
Leukopenia			
subjects affected / exposed	69 / 423 (16.31%)	13 / 427 (3.04%)	
occurrences (all)	226	21	
Thrombocytopenia			
subjects affected / exposed	79 / 423 (18.68%)	25 / 427 (5.85%)	
occurrences (all)	193	36	
Neutropenia			
subjects affected / exposed	274 / 423 (64.78%)	36 / 427 (8.43%)	
occurrences (all)	1299	69	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	51 / 423 (12.06%)	44 / 427 (10.30%)	
occurrences (all)	70	53	
Abdominal pain			
subjects affected / exposed	47 / 423 (11.11%)	60 / 427 (14.05%)	
occurrences (all)	59	83	
Abdominal pain upper			
subjects affected / exposed	28 / 423 (6.62%)	21 / 427 (4.92%)	
occurrences (all)	43	26	
Diarrhoea			
subjects affected / exposed	149 / 423 (35.22%)	137 / 427 (32.08%)	
occurrences (all)	345	265	
Dyspepsia			
subjects affected / exposed	22 / 423 (5.20%)	11 / 427 (2.58%)	
occurrences (all)	32	12	
Stomatitis			

subjects affected / exposed	54 / 423 (12.77%)	50 / 427 (11.71%)	
occurrences (all)	83	64	
Vomiting			
subjects affected / exposed	65 / 423 (15.37%)	42 / 427 (9.84%)	
occurrences (all)	117	52	
Nausea			
subjects affected / exposed	146 / 423 (34.52%)	101 / 427 (23.65%)	
occurrences (all)	346	173	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	5 / 423 (1.18%)	32 / 427 (7.49%)	
occurrences (all)	9	42	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	18 / 423 (4.26%)	23 / 427 (5.39%)	
occurrences (all)	19	27	
Alopecia			
subjects affected / exposed	38 / 423 (8.98%)	5 / 427 (1.17%)	
occurrences (all)	41	5	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	5 / 423 (1.18%)	225 / 427 (52.69%)	
occurrences (all)	5	317	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	27 / 423 (6.38%)	27 / 427 (6.32%)	
occurrences (all)	46	34	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	24 / 423 (5.67%)	29 / 427 (6.79%)	
occurrences (all)	27	29	
Arthralgia			
subjects affected / exposed	23 / 423 (5.44%)	15 / 427 (3.51%)	
occurrences (all)	26	17	
Infections and infestations			
Urinary tract infection			

subjects affected / exposed	31 / 423 (7.33%)	29 / 427 (6.79%)	
occurrences (all)	41	38	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	94 / 423 (22.22%)	76 / 427 (17.80%)	
occurrences (all)	142	97	
Hypomagnesaemia			
subjects affected / exposed	10 / 423 (2.36%)	23 / 427 (5.39%)	
occurrences (all)	14	39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2018	Modification of statistical assumptions based on the results of the primary analysis of the TASCO1 phase 2 study, resulting in a decrease in the study sample size. Update of capecitabine Product Information dated 22 March 2018.
02 April 2020	Modifications of the inclusion criteria: - To consider systemic use of radiosensitizers chemotherapy agents as a previous systemic anticancer therapy for unresectable mCRC - To clarify adequate coagulation function Modifications of the exclusion criteria: -To clarify detection of hepatitis B and C - To clarify other malignancies as exclusion criterion. - radiotherapy (short course for symptoms palliation only) was no more considered as exclusion criteria if completed less than 4 weeks before randomisation Precisions on the study investigational schedule, IMP administration and dose management Clarifications on prohibited treatments Cancellation of the optional genomics biomarkers assessment
25 January 2021	Additional guidance on treatment of study patients in specific situations caused by COVID-19 infection Clarification of reporting rules for fatal adverse events occurring between patient consent signature and the first IMP intake.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported