Clinical trial results:
Randomised study of the efficacy of cetuximab rechallenge in patients with metastatic colorectal cancer (RAS wild-type) responding to first-line treatment with FOLFIRI plus cetuximab

Summary

EudraCT number	2014-003787-21
Trial protocol	DE AT
Global end of trial date	30 December 2024

Results information

Result version number	v1 (current)
This version publication date	29 October 2026
First version publication date	29 October 2026

Trial information

Trial identification

Sponsor protocol code	FIRE-4

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Klinikum der Ludwig-Maximilians-Univ. München
Sponsor organisation address	Marchioninistraße 15, München, Germany, 81377
Public contact	Studiensekretariat, Klinikum der Ludwig-Maximilians-Univ. München, Klinikum Großhadern, 0049 894400 72208, Matthias.Wolff@med.uni-muenchen.de
Scientific contact	Studiensekretariat, Klinikum der Ludwig-Maximilians-Univ. München, Klinikum Großhadern, 0049 894400 72208, Matthias.Wolff@med.uni-muenchen.de

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2026
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 December 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Prospective investigation of overall survival from randomisation to third-line treatment (OS3) under cetuximab rechallenge versus an anti-EGFR-free treatment in patients that have responded to first-line treatment with cetuximab in combination with FOLFIRI or FOLFOX or FOLFOXIRI with CR or PR of any duration or SD ≥ 6 months

Protection of trial subjects:

All study drugs were approved agents used in standard regimens for metastatic colorectal cancer. Toxicities were graded per NCI-CTCAE v4.03, and the protocol specified grade-based dose reduction, delay and discontinuation rules for each drug (e.g. permanent discontinuation of cetuximab after grade 3/4 infusion-related reactions). De-escalation of first-line therapy was permitted in case of toxicity, and treatment breaks at the patient's request or for surgery/radiotherapy were allowed.

To minimise pain and distress, supportive measures were mandated or recommended: premedication with an H1 antihistamine and a corticosteroid before the first cetuximab infusion, a slow initial infusion rate with close monitoring of vital signs for at least two hours; prophylactic doxycycline or minocycline plus basic skin care to reduce cetuximab-induced skin toxicity; prophylactic antiemetics; atropine for irinotecan-related cholinergic syndrome; and a defined loperamide regimen for delayed diarrhoea with clear criteria for hospitalisation. Bevacizumab was paused around surgery to avoid wound-healing complications.

Blood samples for translational research were collected during routine venipunctures. If a repeat tumour biopsy before third-line treatment was infeasible or posed an unacceptable risk, a liquid biopsy could be used instead to confirm RAS wild-type status.

Safety was further ensured by expedited SAE/SUSAR reporting, annual safety reports, on-site monitoring and planned interim safety analyses for first-line and third-line treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 100
Country: Number of subjects enrolled	Germany: 557
Worldwide total number of subjects	657
EEA total number of subjects	657

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)	321
From 65 to 84 years	335
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Part 1 recruited patients in Germany and Austria at 120 sites (111 DE, 9 AT). First patient randomised 11 Aug 2015, last 15 Feb 2021. Planned sample size was increased from 450 to 570 by amendment 6 (Dec 2018). In total, 672 patients were randomised; 657 received study treatment (DE 557, AT 100).

Pre-assignment

Screening details:

Patients had untreated, non-resectable RAS wild-type mCRC, ECOG 0-1, measurable disease and adequate organ function. One prior FOLFIRI cycle was allowed if treatment was urgent. Screening was done within 28 days before randomisation; no wash-out or run-in period. Number of screened patients and screening failures were not recorded.

Period 1

Period 1 title	Part 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A1

Arm description:

FOLFIRI + Cetuximab

Arm type	Active comparator
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

2400 mg/m2 over 46h, starting day 1 on a 2-week-cycle

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:

400mg/m2 day 1 on a 2-week-cycle

Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

400mg/m2 on day 1 of a 2-week-cycle

Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: 180 mg/m2 on day 1 of a 2-week-cycle	
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 on day 1 of 2-week-cycle	
Arm title	Arm B1
Arm description: FOLFIRI + Cetuximab followed by 5-FU/Capecitabine + Bevacizumab	
Arm type	Experimental
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 400 mg/m2 on day 1 of 2-week-cycle	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 2400 mg/m2 starting day 1 of a 2-week-cycle	
Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 on day 1 of a 2-week-cycle	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 180 mg/m2 on day 1 of a 2-week-cycle	
Investigational medicinal product name	Bevcacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 5mg/kg bodyweight on day 1 of a 2-week-cycle	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
1250 mg/m2, twice daily, days 1-4 of a 21-day cycle

Number of subjects in period 1	Arm A1	Arm B1
Started	327	330
Completed	327	330

Period 2

Period 2 title	Part 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A2

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:
2400 mg/m2 over 46h, starting day 1 on a 2-week-cycle

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use

Dosage and administration details:
400mg/m2 day 1 on a 2-week-cycle

Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details: 400mg/m2 on day 1 of a 2-week-cycle	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 180 mg/m2 on day 1 of a 2-week-cycle	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1250 mg/m2, twice daily, days 1-4 of a 21-day cycle	
Investigational medicinal product name	Bevcacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 5mg/kg bodyweight on day 1 of a 2-week-cycle	
Arm title	Arm B2
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use
Dosage and administration details: 2400 mg/m2 over 46h, starting day 1 on a 2-week-cycle	
Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous bolus use
Dosage and administration details: 400mg/m2 day 1 on a 2-week-cycle	
Investigational medicinal product name	Folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400mg/m2 on day 1 of a 2-week-cycle	
Investigational medicinal product name	Irinotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use
Dosage and administration details: 180 mg/m2 on day 1 of a 2-week-cycle	
Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details: 400 mg/m2 on day 1 of 2-week-cycle	

Number of subjects in period 2[1]	Arm A2	Arm B2
Started	47	46
Completed	47	46

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: FIRE-4 consists of two consecutively randomised parts. Therefore, the number of subjects starting Part 2 (n = 93: A2 = 47, B2 = 46) is not expected to equal the number of subjects completing Part 1.

Baseline characteristics

Reporting groups	
Reporting group title	Arm A1
Reporting group description: FOLFIRI + Cetuximab	
Reporting group title	Arm B1
Reporting group description: FOLFIRI + Cetuximab followed by 5-FU/Capecitabine + Bevacizumab	

Reporting group values	Arm A1	Arm B1	Total
Number of subjects	327	330	657
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	154	167	321
From 65-84 years	172	163	335
85 years and over	1	0	1
Gender categorical Units: Subjects			
Female	103	101	204
Male	224	229	453

End points

End points reporting groups

Reporting group title	Arm A1
Reporting group description: FOLFIRI + Cetuximab	
Reporting group title	Arm B1
Reporting group description: FOLFIRI + Cetuximab followed by 5-FU/Capecitabine + Bevacizumab	
Reporting group title	Arm A2
Reporting group description: -	
Reporting group title	Arm B2
Reporting group description: -	

Primary: Overall Survival (OS3)

End point title	Overall Survival (OS3)
End point description:	
End point type	Primary
End point timeframe: From randomisation until death from any cause (patients alive were censored at the last date known to be alive).	

End point values	Arm A2	Arm B2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	45		
Units: month				
median (confidence interval 95%)	15.1 (11.2 to 20.0)	17.6 (12.6 to 21.7)		

Statistical analyses

Statistical analysis title	Arm B2 vs Arm A2
Statistical analysis description: Comparison of overall survival from randomisation between arm B2 and arm A2 using a two-sided log-rank test (alpha = 5 %); hazard ratio estimated by Cox regression.	
Comparison groups	Arm A2 v Arm B2
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.635
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.893

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.558
upper limit	1.429

Secondary: Objective Response rate of first-line treatment (ORR)

End point title	Objective Response rate of first-line treatment (ORR)

End point description:

End point type	Secondary

End point timeframe:

From start of first-line treatment (cycle 1) until 28 days after the last administration of first-line study medication.

End point values	Arm A1	Arm B1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	327	330		
Units: Subjects	206	201		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

.Adverse events were recorded from the first administration of study medication in first-line treatment until 30 days after the last administration. Serious adverse events with a suspected causal relationship to study medication were also reported beyond

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Total cohort

Reporting group description: -

Serious adverse events	Total cohort		
Total subjects affected by serious adverse events			
subjects affected / exposed	311 / 657 (47.34%)		
number of deaths (all causes)	476		
number of deaths resulting from adverse events	28		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour perforation			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour ulceration			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Iliac artery occlusion				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intermittent claudication				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Jugular vein thrombosis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral artery occlusion				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Thromboembolectomy				
subjects affected / exposed	10 / 657 (1.52%)			
occurrences causally related to treatment / all	2 / 10			
deaths causally related to treatment / all	0 / 0			
Thrombophlebitis				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	6 / 657 (0.91%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Laparotomy				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Leg amputation				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Palliative care				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgery				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ureterolysis procedure				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 3			
Device related thrombosis				

subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	5 / 6			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	8 / 657 (1.22%)			
occurrences causally related to treatment / all	5 / 9			
deaths causally related to treatment / all	0 / 0			
Hypothermia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infusion related hypersensitivity reaction				
subjects affected / exposed	8 / 657 (1.22%)			
occurrences causally related to treatment / all	7 / 83			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Oedema peripheral				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Perforation				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	8 / 657 (1.22%)			
occurrences causally related to treatment / all	5 / 10			
deaths causally related to treatment / all	0 / 0			
Sudden cardiac death				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	6 / 657 (0.91%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	0 / 0			
Anaphylactic shock				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug hypersensitivity				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				

Scrotal oedema			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumothorax spontaneous			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Productive cough			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	33 / 657 (5.02%)		
occurrences causally related to treatment / all	5 / 36		
deaths causally related to treatment / all	1 / 3		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Delirium				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Depression suicidal				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Insomnia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
C-reactive protein increased				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutrophil count decreased				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Renal function test abnormal				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Injury, poisoning and procedural complications			
Anastomotic stenosis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ankle fracture			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Contusion			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary bypass stenosis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Craniocerebral injury			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Facial operation			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal stoma complication				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Heat stroke				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Humerus fracture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incisional hernia				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Kidney rupture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lumbar vertebral fracture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic fracture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post procedural bile leak				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal fracture treatment				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Wound dehiscence				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Arteriospasm coronary				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				

subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Cardiac disorder				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Cardiovascular disorder				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Myocardial infarction				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 2			
Myocardial ischaemia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulseless electrical activity				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular dysfunction				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachycardia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid artery stenosis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebellar infarction				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral ischaemia				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	5 / 657 (0.76%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	1 / 1			
Cholinergic syndrome				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhage intracranial				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Headache				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypotonia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Monoparesis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paraesthesia				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Presyncope				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	6 / 657 (0.91%)			
occurrences causally related to treatment / all	6 / 6			
deaths causally related to treatment / all	1 / 1			
Ear and labyrinth disorders				

Vertigo			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ectropion			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal discomfort			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	9 / 657 (1.37%)		
occurrences causally related to treatment / all	5 / 11		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anal haemorrhage			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Colitis ischaemic				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Constipation				
subjects affected / exposed	9 / 657 (1.37%)			
occurrences causally related to treatment / all	3 / 9			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	33 / 657 (5.02%)			
occurrences causally related to treatment / all	37 / 40			
deaths causally related to treatment / all	0 / 0			
Duodenal stenosis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enteritis				
subjects affected / exposed	7 / 657 (1.07%)			
occurrences causally related to treatment / all	6 / 83			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gastritis				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic ascites				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemorrhoids thrombosed				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	19 / 657 (2.89%)			
occurrences causally related to treatment / all	1 / 19			
deaths causally related to treatment / all	0 / 3			
Ileus paralytic				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal perforation				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Large intestinal stenosis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Large intestine perforation				

subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Mechanical ileus				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Oesophagitis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatic cyst rupture				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proctalgia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proctitis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal perforation				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mucositis management				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subileus				
subjects affected / exposed	7 / 657 (1.07%)			
occurrences causally related to treatment / all	0 / 83			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cholestasis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic failure				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	1 / 2			
Skin and subcutaneous tissue disorders				

Dermatitis				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Dermatitis acneiform				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug eruption				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erythema				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Exanthema subitum				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Palmar-plantar erythrodysaesthesia syndrome				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Skin ulcer				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				

Acute kidney injury				
subjects affected / exposed	7 / 657 (1.07%)			
occurrences causally related to treatment / all	5 / 83			
deaths causally related to treatment / all	0 / 0			
Prerenal failure				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Haematuria				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal colic				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	4 / 5			
deaths causally related to treatment / all	0 / 0			
Renal pelvis fistula				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urethral obstruction				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Urethritis noninfective				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary retention				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Urinary tract obstruction				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Bursitis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteochondrosis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal pain				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Abdominal abscess				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abscess				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacterial translocation				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				

subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Campylobacter gastroenteritis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium colitis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Device related infection				
subjects affected / exposed	15 / 657 (2.28%)			
occurrences causally related to treatment / all	2 / 19			
deaths causally related to treatment / all	0 / 0			
Device related sepsis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Endocarditis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Erysipelas				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Escherichia sepsis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 2			
Febrile infection				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis norovirus				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal infection				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Infected bite				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infected dermal cyst				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	148 / 657 (22.53%)			
occurrences causally related to treatment / all	8 / 14			
deaths causally related to treatment / all	0 / 0			
Colitis				

subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	5 / 657 (0.76%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Lung infiltration				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Neutropenic sepsis				
subjects affected / exposed	3 / 657 (0.46%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pancreas infection				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Paronychia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic abscess				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	4 / 657 (0.61%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	15 / 657 (2.28%)			
occurrences causally related to treatment / all	2 / 15			
deaths causally related to treatment / all	1 / 4			
Purulent discharge				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal abscess				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	6 / 657 (0.91%)			
occurrences causally related to treatment / all	2 / 6			
deaths causally related to treatment / all	0 / 2			
Septic encephalopathy				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Soft tissue infection				

subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stoma site abscess				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Stoma site infection				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Superinfection				
subjects affected / exposed	1 / 657 (0.15%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	11 / 657 (1.67%)			
occurrences causally related to treatment / all	5 / 11			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	2 / 657 (0.30%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				

subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	4 / 657 (0.61%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Hypercreatininaemia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	3 / 657 (0.46%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			
subjects affected / exposed	2 / 657 (0.30%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Hypovolaemia			
subjects affected / exposed	1 / 657 (0.15%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total cohort		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	616 / 657 (93.76%)		
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	33 / 657 (5.02%)		
occurrences (all)	48		
Weight decreased			
subjects affected / exposed	105 / 657 (15.98%)		
occurrences (all)	123		
Weight increased			
subjects affected / exposed	33 / 657 (5.02%)		
occurrences (all)	41		
Vascular disorders			
Hypertension			
subjects affected / exposed	95 / 657 (14.46%)		
occurrences (all)	138		
Thrombosis			
subjects affected / exposed	34 / 657 (5.18%)		
occurrences (all)	36		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	37 / 657 (5.63%)		
occurrences (all)	50		
Paraesthesia			
subjects affected / exposed	78 / 657 (11.87%)		
occurrences (all)	109		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	66 / 657 (10.05%)		
occurrences (all)	83		
Leukopenia			
subjects affected / exposed	87 / 657 (13.24%)		
occurrences (all)	183		

Neutropenia			
subjects affected / exposed	148 / 657 (22.53%)		
occurrences (all)	280		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	233 / 657 (35.46%)		
occurrences (all)	354		
Infusion related hypersensitivity reaction			
subjects affected / exposed	40 / 657 (6.09%)		
occurrences (all)	42		
Oedema peripheral			
subjects affected / exposed	39 / 657 (5.94%)		
occurrences (all)	53		
Pain			
subjects affected / exposed	139 / 657 (21.16%)		
occurrences (all)	191		
Pyrexia			
subjects affected / exposed	43 / 657 (6.54%)		
occurrences (all)	44		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	34 / 657 (5.18%)		
occurrences (all)	50		
Constipation			
subjects affected / exposed	88 / 657 (13.39%)		
occurrences (all)	114		
Diarrhoea			
subjects affected / exposed	329 / 657 (50.08%)		
occurrences (all)	695		
Dyspepsia			
subjects affected / exposed	37 / 657 (5.63%)		
occurrences (all)	39		
Mucositis management			
subjects affected / exposed	224 / 657 (34.09%)		
occurrences (all)	243		
Nausea			

subjects affected / exposed	210 / 657 (31.96%)		
occurrences (all)	342		
Vomiting			
subjects affected / exposed	83 / 657 (12.63%)		
occurrences (all)	116		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	46 / 657 (7.00%)		
occurrences (all)	59		
Epistaxis			
subjects affected / exposed	42 / 657 (6.39%)		
occurrences (all)	57		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	140 / 657 (21.31%)		
occurrences (all)	161		
Dry skin			
subjects affected / exposed	138 / 657 (21.00%)		
occurrences (all)	189		
Exanthema subitum			
subjects affected / exposed	339 / 657 (51.60%)		
occurrences (all)	844		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	134 / 657 (20.40%)		
occurrences (all)	203		
Pruritus			
subjects affected / exposed	51 / 657 (7.76%)		
occurrences (all)	70		
Rash			
subjects affected / exposed	160 / 657 (24.35%)		
occurrences (all)	255		
Skin fissures			
subjects affected / exposed	153 / 657 (23.29%)		
occurrences (all)	227		
Infections and infestations			

Conjunctivitis subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all) Paronychia subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	53 / 657 (8.07%) 70 72 / 657 (10.96%) 94 95 / 657 (14.46%) 119 36 / 657 (5.48%) 46		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	73 / 657 (11.11%) 107 67 / 657 (10.20%) 121 73 / 657 (11.11%) 122		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 September 2015	Amendment 1
27 April 2016	Amendment 2
17 February 2017	Amendment 3
18 December 2017	Amendment 4
08 March 2018	Amendment 5
21 December 2018	Amendment 6
02 May 2019	Amendment 7
12 July 2019	Amendment 8
02 February 2021	Amendment 9

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported