Clinical trial results:
A Phase 3, Multicenter, Open-label, Randomized Study of nab-Paclitaxel Plus Gemcitabine Versus Gemcitabine Alone as Adjuvant Therapy in Subjects With Surgically Resected Pancreatic Adenocarcinoma

Summary

EudraCT number	2013-003398-91
Trial protocol	CZ AT HU ES IT PT BE FI IE DK GB NL
Global end of trial date	30 June 2022

Results information

Result version number	v1 (current)
This version publication date	29 June 2023
First version publication date	29 June 2023

Trial information

Trial identification

Sponsor protocol code	ABI-007-PANC-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01964430
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare disease-free survival (DFS) between subjects randomized to nabpaclitaxel in combination with gemcitabine and subjects randomized to gemcitabine
alone

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 31
Country: Number of subjects enrolled	United States: 269
Country: Number of subjects enrolled	Austria: 27
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	Finland: 19
Country: Number of subjects enrolled	France: 37
Country: Number of subjects enrolled	Germany: 85
Country: Number of subjects enrolled	Hungary: 19
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Italy: 106
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Spain: 54
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Australia: 50
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Korea, Republic of: 51

Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Taiwan: 47
Worldwide total number of subjects	866
EEA total number of subjects	398

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)	446
From 65 to 84 years	419
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study randomized participants at 160 sites in 21 countries: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Hong Kong, Hungary, Ireland, Italy, Netherlands, Portugal, Singapore, Republic of Korea, Spain, Taiwan, United Kingdom and the US.

Pre-assignment

Screening details:

Participants were randomized using a stratified randomization with a 1:1 ratio to either nab-paclitaxel followed by gemcitabine, or gemcitabine alone. Stratification factors were tumor resection status (R0 versus R1), nodal status lymph node positive versus lymph node negative, and region [North America, Europe, and Australia versus Asia Pacific]).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	nab-Paclitaxel and Gemcitabine

Arm description:

Participants received nab-Paclitaxel 125 mg/m^2 administered as an intravenous (IV) infusion over 30 to 40 minutes, followed by gemcitabine 1000 mg/m^2 as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m2 as a 30- to 40-minute infusion

Investigational medicinal product name	nab-Paclitaxel
Investigational medicinal product code	
Other name	ABRAXANE
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

125 mg/m2 as a 30- to 40-minute infusion

Arm title	Gemcitabine

Arm description:

Participants received gemcitabine 1000 mg/m^2 administered as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Arm type	Experimental

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

Dosage and administration details:

1000 mg/m2 as a 30- to 40-minute infusion

Number of subjects in period 1	nab-Paclitaxel and Gemcitabine	Gemcitabine
Started	432	434
Completed	429	423
Not completed	3	11
Consent withdrawn by subject	2	9
Adverse event, non-fatal	1	-
Protocol Deviation	-	2

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	nab-Paclitaxel and Gemcitabine

Arm description:

Participants received nab-Paclitaxel 125 mg/m^2 administered as an intravenous (IV) infusion over 30 to 40 minutes, followed by gemcitabine 1000 mg/m^2 as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m2 as a 30- to 40-minute infusion

Investigational medicinal product name	nab-Paclitaxel
Investigational medicinal product code	
Other name	ABRAXANE
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

125 mg/m2 as a 30- to 40-minute infusion

Arm title	Gemcitabine

Arm description:

Participants received gemcitabine 1000 mg/m^2 administered as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Arm type	Experimental
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1000 mg/m2 as a 30- to 40-minute infusion

Number of subjects in period 2	nab-Paclitaxel and Gemcitabine	Gemcitabine
Started	429	423
Completed	287	310
Not completed	142	113
Adverse event, serious fatal	1	3
Consent withdrawn by subject	36	27
Physician decision	5	4
Disease Relapse	28	38
Adverse event, non-fatal	71	37
Protocol Deviation	-	1
Other reasons	1	3

Baseline characteristics

Reporting groups	
Reporting group title	nab-Paclitaxel and Gemcitabine
Reporting group description:	
Participants received nab-Paclitaxel 125 mg/m^2 administered as an intravenous (IV) infusion over 30 to 40 minutes, followed by gemcitabine 1000 mg/m^2 as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.	
Reporting group title	Gemcitabine
Reporting group description:	
Participants received gemcitabine 1000 mg/m^2 administered as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.	

Reporting group values	nab-Paclitaxel and Gemcitabine	Gemcitabine	Total
Number of subjects	432	434	866
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)	221	225	446
From 65-84 years	211	208	419
85 years and over	0	1	1
Age Continuous Units: Years			
arithmetic mean	63.4	62.9	
standard deviation	± 9.58	± 8.84	-
Sex: Female, Male Units: Participants			
Female	204	181	385
Male	228	253	481
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	11	15	26
Not Hispanic or Latino	400	393	793
Unknown or Not Reported	21	26	47
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	60	56	116
Black or African American	4	8	12
Native Hawaiian or Other Pacific Islander	0	2	2
White	333	339	672

Other	11	6	17
Not Collected or Reported	24	22	46
Region of Enrollment Units: Subjects			
North America	144	156	300
Europe	203	205	408
Australia	30	20	50
Asia Pacific	55	53	108
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status is used to describe a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). The scale ranges from 0 to 5: 0 = Fully active, no restrictions; 1 = Restricted activity but ambulatory, able to carry out work of a light nature; 2 = Ambulatory and capable of all self-care but unable to carry out work activities; 3 = Limited self-care, confined to bed or chair more than 50% of waking hours; 4 = Completely disabled, no self-care, confined to bed or chair; 5 = Dead			
Units: Subjects			
0 = Fully Active	252	268	520
1 = Restricted but Ambulatory	180	166	346
2 = Ambulatory but Unable to Work	0	0	0
3 = Limited Self-care	0	0	0
4 = Completely Disabled	0	0	0
Physician Assessment of Peripheral Neuropathy			
Physician assessment for grading of peripheral neuropathy in participants receiving chemotherapy according to National Cancer Institute Common Toxicity Criteria (NCICTC): - Grade 1 = Asymptomatic: loss of deep tendon reflexes or paresthesia; - Grade 2 = Moderate symptoms: limiting instrumental Activities of Daily Living (ADLs); - Grade 3 = Severe symptoms: limiting self-care ADL; assistance device indicated; - Grade 4 = Life-threatening consequences: urgent intervention indicated.			
Units: Subjects			
Grade 0	404	408	812
Grade 1	26	21	47
Grade 2	0	1	1
Grade 3	0	0	0
Grade 4	0	0	0
Missing	2	4	6
TNM Classification			
The TNM system is the most widely used cancer staging system. Most hospitals and medical centers use the TNM system as their main method for cancer reporting. In the TNM system: The T refers to the size and extent of the main tumor. The main tumor is usually called the primary tumor and the "T" followed by a number shows the size of the tumor. The N refers to the number of nearby lymph nodes that have cancer. The M refers to whether the cancer has metastasized. This means that the cancer has spread from the primary tumor to other parts of the body.			
Units: Subjects			
T1 = Tumor is 2 cm or smaller	16	13	29
T2 = Tumor is > 2 cm, but not larger than 5 cm	38	37	75
T3 = Tumor is larger than 5 cm	377	384	761
T4 = Tumor is any size, but has spread	1	0	1
Nodal Status			
The nodal status refers to the N and includes the number of nearby lymph nodes that are positive or negative for cancer.			
Units: Subjects			
Lymph Node Positive (LN+)	311	312	623
Lymph Node Negative (LN-)	121	122	243
Resection Status			

Resection status was based on investigational site data (pathology reports were collected, but central pathology review and/or standardization was not conducted).			
Units: Subjects			
R0 (tumor-negative resection margin)	327	334	661
R1 (tumor- positive resection margin)	105	100	205
Time from Surgery to Randomization			
Units: Days			
median	57.0	56.0	
full range (min-max)	23.0 to 90.0	17.0 to 88.0	-
Body Surface Area (BSA)			
Units: m²			
arithmetic mean	1.77	1.78	
standard deviation	± 0.226	± 0.221	-

End points

End points reporting groups

Reporting group title	nab-Paclitaxel and Gemcitabine

Reporting group description:

Participants received nab-Paclitaxel 125 mg/m^2 administered as an intravenous (IV) infusion over 30 to 40 minutes, followed by gemcitabine 1000 mg/m^2 as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Reporting group title	Gemcitabine

Reporting group description:

Participants received gemcitabine 1000 mg/m^2 administered as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Reporting group title	nab-Paclitaxel and Gemcitabine

Reporting group description:

Participants received nab-Paclitaxel 125 mg/m^2 administered as an intravenous (IV) infusion over 30 to 40 minutes, followed by gemcitabine 1000 mg/m^2 as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Reporting group title	Gemcitabine

Reporting group description:

Participants received gemcitabine 1000 mg/m^2 administered as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Primary: Kaplan Meier Estimate for Disease Free Survival (DFS) According to the Independent Radiological Review Committee

End point title	Kaplan Meier Estimate for Disease Free Survival (DFS) According to the Independent Radiological Review Committee

End point description:

Disease free survival was defined as the time from the date of randomization to the date of disease recurrence or death, whichever occurred earlier. Disease recurrence was determined by the independent radiological review of computed tomography (CT) or magnetic resonance imaging (MRI) scans. Participants who did not have disease recurrence or did not die were censored at the last tumor assessment date with disease-free status or the randomization date if the last tumor assessment with disease-free status was missing. Disease-free status referred to a status that was neither being disease recurrent nor indeterminate or not evaluable. Participants who received new anti-cancer therapy or cancer-related surgery prior to disease recurrence or death were censored at the date of last tumor assessment with disease-free status prior to the start of new anti-cancer therapy or cancer-related surgery or the randomization date.

End point type	Primary

End point timeframe:

Date of randomization up to data cut off date of 31 December 2018; median DFS follow-up time for censored participants was 22.242 months for nab-Paclitaxel and gemcitabine and 13.832 months for gemcitabine alone

End point values	nab-Paclitaxel and Gemcitabine	Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	434		
Units: months				
median (confidence interval 95%)	19.4 (16.62 to 21.91)	18.8 (13.83 to 20.30)		

Statistical analyses

Statistical analysis title	Disease Free Survival (DFS)
Comparison groups	nab-Paclitaxel and Gemcitabine v Gemcitabine
Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1824
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.729
upper limit	1.063

Secondary: Kaplan Meier Estimate of Overall Survival (OS)

End point title	Kaplan Meier Estimate of Overall Survival (OS)

End point description:

Overall survival was defined as the time from the date of randomization to the date of death. Participants who were alive at the end of study or clinical data cut were censored on the last-known-to-be-alive date or the clinical cutoff date, whichever was earlier. 99999 = N/A - insufficient number of participants with events.

End point type	Secondary

End point timeframe:

From randomization to date of death; median OS follow-up time for censored participants was 77.832 months for nab-Paclitaxel and gemcitabine and 77.799 months for gemcitabine alone

End point values	nab-Paclitaxel and Gemcitabine	Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	432	434		
Units: months				
median (confidence interval 95%)				
25th Quartile	20.7 (19.38 to 22.83)	17.7 (14.78 to 19.91)		

50th Quartile	41.8 (35.55 to 47.28)	37.7 (31.11 to 40.51)		
75th Quartile	90.2 (83.55 to 99999)	83.0 (61.93 to 99999)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	nab-Paclitaxel and Gemcitabine v Gemcitabine
Number of subjects included in analysis	866
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0128
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.691
upper limit	0.957

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAE's)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAE's)

End point description:

TEAEs are defined as any adverse event (AE) that begin or worsen on or after the start of study drug or procedure of the study period through the maximum duration of the period plus 28 days. The severity of AEs was graded based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 and the scale: Grade 1 = Mild Grade 2 = Moderate Grade 3 = Severe Grade 4 = Life threatening Grade 5 = Death. Relation to study drug was determined by the investigator. A treatment-related TEAE is defined as TEAE which was considered to be related to one or both of the study drugs and reported as 'Suspected' on the case report form. AEs with a missing relationship were treated as 'treatment-related' in data summaries. IP (investigational product) refers to nab-Paclitaxel and/or Gemcitabine. "Related" TEAE refers to relation to study drug (IP).

End point type	Secondary

End point timeframe:

From day 1 of study drug up to 28 days after the last dose of study drug; up to the data cut off date of 31 December 2018 (up to approximately 37 weeks).

End point values	nab-Paclitaxel and Gemcitabine	Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Participants				
≥1 TEAE	429	417		

≥1 Related TEAE	423	399		
≥1 TEAE of Severity Grade 3 or Higher	371	286		
≥ 1 Related TEAE of Severity Grade 3 or Higher	332	239		
≥1 Serious TEAE	176	96		
≥1 Serious Related TEAE	102	55		
≥1 TEAE Leading to Withdrawal of IP	117	43		
≥1 Related TEAE Leading to Withdrawal of IP	98	35		
≥1 TEAE Lead Dose Reduction: nab-Paclitaxel or Gem	276	210		
≥1 Related TEAE Dose Reduct: nab-Paclitaxel or Gem	270	205		
TEAE Lead Dose Interruption nab-Paclitaxel or Gem	266	158		
≥1 Related TEAE Dose Interruption to IP	221	125		
TEAE Leading to Death	2	2		
>=1 Related TEAE Leading to Death	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Clinical Chemistry Laboratory-Detected Abnormalities (Grade 3-4)

End point title	The Number of Participants with Clinical Chemistry Laboratory-Detected Abnormalities (Grade 3-4)

End point description:

The number of participants with grade 3-4 laboratory abnormalities in selected clinically significant parameters. Grades for chemistry parameters were coded using National Cancer Institute Common Terminology Criteria for Adverse Events (Grade 3= severe, Grade 4= life-threatening).

End point type	Secondary

End point timeframe:

From day 1 of study drug up to 28 days after the last dose of study drug, or the treatment discontinuation date, whichever was later (up to approximately 37 weeks).

End point values	nab-Paclitaxel and Gemcitabine	Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	421	416		
Units: Participants				
Alkaline phosphatase	7	3		
Alanine aminotransferase	9	3		
Aspartate aminotransferase	9	2		
Bilirubin	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs and NSAEs were assessed from first dose to 100 days following last dose (up to approximately 46 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Gemcitabine

Reporting group description:

Participants received gemcitabine 1000 mg/m^2 administered as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Reporting group title	nab-Paclitaxel and Gemcitabine

Reporting group description:

Participants received nab-Paclitaxel 125 mg/m^2 administered as an intravenous (IV) infusion over 30 to 40 minutes, followed by gemcitabine 1000 mg/m^2 as an IV infusion over 30 to 40 minutes on Days 1, 8 and 15 of each 28-day treatment cycle for 6 cycles, unless there was evidence of radiologic disease recurrence, unacceptable toxicity, subject or physician decision, withdrawal of consent, or death.

Serious adverse events	Gemcitabine	nab-Paclitaxel and Gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	96 / 423 (22.70%)	181 / 429 (42.19%)	
number of deaths (all causes)	294	284	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour inflammation			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 423 (0.71%)	5 / 429 (1.17%)	
occurrences causally related to treatment / all	0 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillary leak syndrome			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 423 (0.24%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 423 (0.47%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 423 (0.47%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			

subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (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 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 423 (0.24%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	2 / 423 (0.47%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 423 (0.00%)	7 / 429 (1.63%)	
occurrences causally related to treatment / all	0 / 0	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			

subjects affected / exposed	3 / 423 (0.71%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	3 / 423 (0.71%)	5 / 429 (1.17%)	
occurrences causally related to treatment / all	0 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyserositis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	24 / 423 (5.67%)	29 / 429 (6.76%)	
occurrences causally related to treatment / all	0 / 32	16 / 41	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	3 / 423 (0.71%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (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			
Cough			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 423 (0.47%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 423 (1.18%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 5	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			

subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (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	5 / 423 (1.18%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 423 (0.47%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 423 (0.71%)	5 / 429 (1.17%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 423 (0.47%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			

subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram ST segment elevation			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave inversion			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Liver function test increased			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural inflammation			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incisional hernia			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripancreatic fluid collection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fistula			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	2 / 423 (0.47%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion-related circulatory overload			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial rupture			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	2 / 423 (0.47%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	2 / 423 (0.47%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	4 / 423 (0.95%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	2 / 423 (0.47%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 423 (0.47%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 423 (0.24%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 423 (0.24%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 423 (1.42%)	12 / 429 (2.80%)	
occurrences causally related to treatment / all	0 / 6	9 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 423 (0.71%)	5 / 429 (1.17%)	
occurrences causally related to treatment / all	0 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	2 / 423 (0.47%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microangiopathic haemolytic anaemia			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 423 (0.71%)	16 / 429 (3.73%)	
occurrences causally related to treatment / all	0 / 3	15 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 423 (0.24%)	5 / 429 (1.17%)	
occurrences causally related to treatment / all	0 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	2 / 423 (0.47%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	2 / 423 (0.47%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intra-abdominal fluid collection			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			

subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	4 / 423 (0.95%)	7 / 429 (1.63%)	
occurrences causally related to treatment / all	0 / 4	3 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal incontinence			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer perforation			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 423 (0.47%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 423 (0.00%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 423 (0.00%)	12 / 429 (2.80%)	
occurrences causally related to treatment / all	0 / 0	9 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal hernia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (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	0 / 423 (0.00%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal perforation			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 423 (0.00%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	3 / 423 (0.71%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal haemorrhage			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	1 / 423 (0.24%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 423 (0.24%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 423 (0.24%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 423 (0.00%)	8 / 429 (1.86%)	
occurrences causally related to treatment / all	0 / 0	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	3 / 423 (0.71%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	0 / 423 (0.00%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (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%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 423 (0.47%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscle atrophy			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (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	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 423 (0.00%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	

Appendicitis			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis clostridial			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	5 / 423 (1.18%)	8 / 429 (1.86%)	
occurrences causally related to treatment / all	0 / 5	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholera			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 423 (0.00%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	2 / 423 (0.47%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 423 (0.00%)	4 / 429 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (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	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 423 (0.24%)	9 / 429 (2.10%)	
occurrences causally related to treatment / all	0 / 1	9 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 423 (0.00%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic abscess			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	6 / 423 (1.42%)	9 / 429 (2.10%)	
occurrences causally related to treatment / all	0 / 6	5 / 10	
deaths causally related to treatment / all	0 / 1	0 / 2	
Post procedural infection			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth infection			
subjects affected / exposed	1 / 423 (0.24%)	0 / 429 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 423 (0.47%)	7 / 429 (1.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 423 (0.00%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 423 (1.18%)	12 / 429 (2.80%)	
occurrences causally related to treatment / all	0 / 5	9 / 13	
deaths causally related to treatment / all	0 / 1	1 / 1	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 423 (0.47%)	8 / 429 (1.86%)	
occurrences causally related to treatment / all	0 / 2	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid retention			
subjects affected / exposed	1 / 423 (0.24%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	1 / 423 (0.24%)	3 / 429 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	2 / 423 (0.47%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 423 (0.00%)	2 / 429 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 423 (0.00%)	1 / 429 (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	Gemcitabine	nab-Paclitaxel and Gemcitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	407 / 423 (96.22%)	426 / 429 (99.30%)	
Investigations			
Weight decreased			
subjects affected / exposed	22 / 423 (5.20%)	52 / 429 (12.12%)	
occurrences (all)	22	60	
Neutrophil count decreased			

subjects affected / exposed	32 / 423 (7.57%)	23 / 429 (5.36%)	
occurrences (all)	69	51	
Blood alkaline phosphatase increased			
subjects affected / exposed	17 / 423 (4.02%)	23 / 429 (5.36%)	
occurrences (all)	24	34	
Aspartate aminotransferase increased			
subjects affected / exposed	21 / 423 (4.96%)	31 / 429 (7.23%)	
occurrences (all)	31	46	
Alanine aminotransferase increased			
subjects affected / exposed	33 / 423 (7.80%)	42 / 429 (9.79%)	
occurrences (all)	51	54	
Vascular disorders			
Hypotension			
subjects affected / exposed	12 / 423 (2.84%)	30 / 429 (6.99%)	
occurrences (all)	14	37	
Hypertension			
subjects affected / exposed	49 / 423 (11.58%)	35 / 429 (8.16%)	
occurrences (all)	70	51	
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	26 / 423 (6.15%)	112 / 429 (26.11%)	
occurrences (all)	30	128	
Headache			
subjects affected / exposed	66 / 423 (15.60%)	65 / 429 (15.15%)	
occurrences (all)	90	91	
Dysgeusia			
subjects affected / exposed	36 / 423 (8.51%)	86 / 429 (20.05%)	
occurrences (all)	39	95	
Dizziness			
subjects affected / exposed	34 / 423 (8.04%)	64 / 429 (14.92%)	
occurrences (all)	39	77	
Paraesthesia			
subjects affected / exposed	9 / 423 (2.13%)	39 / 429 (9.09%)	
occurrences (all)	9	50	
Polyneuropathy			

subjects affected / exposed	6 / 423 (1.42%)	23 / 429 (5.36%)	
occurrences (all)	8	27	
Peripheral sensory neuropathy			
subjects affected / exposed	16 / 423 (3.78%)	144 / 429 (33.57%)	
occurrences (all)	20	177	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	203 / 423 (47.99%)	233 / 429 (54.31%)	
occurrences (all)	315	350	
Asthenia			
subjects affected / exposed	49 / 423 (11.58%)	95 / 429 (22.14%)	
occurrences (all)	116	192	
Chills			
subjects affected / exposed	23 / 423 (5.44%)	38 / 429 (8.86%)	
occurrences (all)	27	63	
Pyrexia			
subjects affected / exposed	115 / 423 (27.19%)	171 / 429 (39.86%)	
occurrences (all)	194	369	
Peripheral swelling			
subjects affected / exposed	16 / 423 (3.78%)	22 / 429 (5.13%)	
occurrences (all)	21	24	
Oedema peripheral			
subjects affected / exposed	108 / 423 (25.53%)	162 / 429 (37.76%)	
occurrences (all)	130	207	
Influenza like illness			
subjects affected / exposed	25 / 423 (5.91%)	27 / 429 (6.29%)	
occurrences (all)	53	41	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	85 / 423 (20.09%)	94 / 429 (21.91%)	
occurrences (all)	174	212	
Neutropenia			
subjects affected / exposed	230 / 423 (54.37%)	263 / 429 (61.31%)	
occurrences (all)	568	638	
Leukopenia			

subjects affected / exposed	72 / 423 (17.02%)	84 / 429 (19.58%)	
occurrences (all)	151	201	
Anaemia			
subjects affected / exposed	142 / 423 (33.57%)	179 / 429 (41.72%)	
occurrences (all)	214	267	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	192 / 423 (45.39%)	231 / 429 (53.85%)	
occurrences (all)	321	431	
Dyspepsia			
subjects affected / exposed	24 / 423 (5.67%)	21 / 429 (4.90%)	
occurrences (all)	25	21	
Diarrhoea			
subjects affected / exposed	125 / 423 (29.55%)	242 / 429 (56.41%)	
occurrences (all)	183	458	
Constipation			
subjects affected / exposed	89 / 423 (21.04%)	114 / 429 (26.57%)	
occurrences (all)	112	150	
Abdominal pain upper			
subjects affected / exposed	40 / 423 (9.46%)	35 / 429 (8.16%)	
occurrences (all)	47	38	
Abdominal pain			
subjects affected / exposed	87 / 423 (20.57%)	119 / 429 (27.74%)	
occurrences (all)	100	158	
Stomatitis			
subjects affected / exposed	24 / 423 (5.67%)	81 / 429 (18.88%)	
occurrences (all)	35	102	
Vomiting			
subjects affected / exposed	77 / 423 (18.20%)	122 / 429 (28.44%)	
occurrences (all)	140	208	
Flatulence			
subjects affected / exposed	27 / 423 (6.38%)	23 / 429 (5.36%)	
occurrences (all)	31	25	
Respiratory, thoracic and mediastinal disorders			

Oropharyngeal pain			
subjects affected / exposed	18 / 423 (4.26%)	28 / 429 (6.53%)	
occurrences (all)	18	34	
Epistaxis			
subjects affected / exposed	13 / 423 (3.07%)	76 / 429 (17.72%)	
occurrences (all)	14	101	
Dyspnoea			
subjects affected / exposed	50 / 423 (11.82%)	65 / 429 (15.15%)	
occurrences (all)	57	71	
Cough			
subjects affected / exposed	51 / 423 (12.06%)	61 / 429 (14.22%)	
occurrences (all)	55	73	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	20 / 423 (4.73%)	35 / 429 (8.16%)	
occurrences (all)	27	46	
Rash			
subjects affected / exposed	20 / 423 (4.73%)	49 / 429 (11.42%)	
occurrences (all)	23	62	
Pruritus			
subjects affected / exposed	20 / 423 (4.73%)	37 / 429 (8.62%)	
occurrences (all)	22	40	
Alopecia			
subjects affected / exposed	52 / 423 (12.29%)	252 / 429 (58.74%)	
occurrences (all)	55	264	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	34 / 423 (8.04%)	64 / 429 (14.92%)	
occurrences (all)	35	72	
Anxiety			
subjects affected / exposed	38 / 423 (8.98%)	34 / 429 (7.93%)	
occurrences (all)	38	35	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	33 / 423 (7.80%)	45 / 429 (10.49%)	
occurrences (all)	36	56	

Myalgia			
subjects affected / exposed	29 / 423 (6.86%)	57 / 429 (13.29%)	
occurrences (all)	42	72	
Muscular weakness			
subjects affected / exposed	6 / 423 (1.42%)	25 / 429 (5.83%)	
occurrences (all)	7	33	
Bone pain			
subjects affected / exposed	15 / 423 (3.55%)	23 / 429 (5.36%)	
occurrences (all)	16	27	
Back pain			
subjects affected / exposed	44 / 423 (10.40%)	41 / 429 (9.56%)	
occurrences (all)	49	55	
Arthralgia			
subjects affected / exposed	31 / 423 (7.33%)	68 / 429 (15.85%)	
occurrences (all)	37	89	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	20 / 423 (4.73%)	29 / 429 (6.76%)	
occurrences (all)	27	32	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	84 / 423 (19.86%)	143 / 429 (33.33%)	
occurrences (all)	97	167	
Dehydration			
subjects affected / exposed	8 / 423 (1.89%)	28 / 429 (6.53%)	
occurrences (all)	10	39	
Hypokalaemia			
subjects affected / exposed	23 / 423 (5.44%)	55 / 429 (12.82%)	
occurrences (all)	34	77	
Hyperglycaemia			
subjects affected / exposed	28 / 423 (6.62%)	34 / 429 (7.93%)	
occurrences (all)	39	55	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2014	Significant changes included: Regional stratification, sample size calculating, assessment of disease recurrence, and eligibility.
03 December 2015	Clarification on how to define a subject that has completed 6 cycles of study treatment versus discontinued early from study treatment, what is considered to be new/subsequent anticancer therapy, and dose modifications. Updated treatment administration and schedule section to include flushing requirement.
21 December 2016	Removal of the second interim analysis of efficacy and modification of stratification by Region.
12 September 2018	Revised the final disease-free survival (DFS) analysis to be earlier than was originally planned (489 events).
03 September 2019	Revise the protocol procedures to be performed after achieving the primary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported