



Clinical trial results:

A Phase III Study of BBI-608 plus nab-Paclitaxel with Gemcitabine in Adult Patients with Metastatic Pancreatic Adenocarcinoma.

Summary

EudraCT number	2016-004359-57
Trial protocol	DE ES NL BE CZ AT PT PL IT
Global end of trial date	29 March 2020

Results information

Result version number	v1 (current)
This version publication date	16 April 2021
First version publication date	16 April 2021

Trial information

Trial identification

Sponsor protocol code	CanStem111P
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02993731
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sumitomo Dainippon Pharma Oncology
Sponsor organisation address	640 Memorial Drive, Cambridge, United States, 02139
Public contact	Cindy Oh, Sumitomo Dainippon Pharma Oncology, 1 6176748625, coh@bostonbiomedical.com
Scientific contact	Cindy Oh, Sumitomo Dainippon Pharma Oncology, 1 6176748625, coh@bostonbiomedical.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	15 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2020
Global end of trial reached?	Yes
Global end of trial date	29 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare overall survival (OS) of patients with metastatic pancreatic adenocarcinoma (PDAC) treated with BBI-608 plus weekly nab-paclitaxel with gemcitabine (Arm 1) versus weekly nab-paclitaxel with gemcitabine (Arm 2).

Protection of trial subjects:

The study was conducted in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines, and applicable local laws and national regulations relevant to the use of new therapeutic agents in the country of conduct. Patients who could not given informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) were not recruited to this study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Poland: 41
Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Spain: 66
Country: Number of subjects enrolled	Austria: 23
Country: Number of subjects enrolled	Belgium: 32
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	France: 52
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 53
Country: Number of subjects enrolled	Australia: 47
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	China: 115
Country: Number of subjects enrolled	Japan: 119
Country: Number of subjects enrolled	Russian Federation: 57
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Korea, Republic of: 99
Country: Number of subjects enrolled	Taiwan: 29

Country: Number of subjects enrolled	Ukraine: 25
Country: Number of subjects enrolled	United States: 314
Worldwide total number of subjects	1134
EEA total number of subjects	315

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)	620
From 65 to 84 years	511
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

1134 participants were randomized globally between February 2017 and February 2019.

Pre-assignment

Screening details:

Baseline evaluations were performed for all patients <14 days prior to randomization to determine study eligibility. A total of 1779 screenings were recorded.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Napabucasin plus Nab-paclitaxel with Gemcitabine

Arm description:

All participants who were randomized to Arm 1 to receive napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.

Arm type	Experimental
Investigational medicinal product name	Napabucasin
Investigational medicinal product code	
Other name	BBI608, BBI-608
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Napabucasin was administered orally, twice daily, with doses separated by approximately 12 hours. Napabucasin administration began 2-5 days prior to the first nab-paclitaxel with gemcitabine infusion.

Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel 125 mg/m² immediately followed by gemcitabine 1000 mg/m² were administered on Days 1, 8 and 15 of every 28-day cycle via intravenous infusion.

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

Dosage and administration details:

Nab-paclitaxel 125 mg/m² immediately followed by gemcitabine 1000 mg/m² were administered on Days 1, 8 and 15 of every 28-day cycle via intravenous infusion.

Arm title	Nab-paclitaxel with Gemcitabine
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Arm description:

All participants who were randomized to Arm 2 to receive nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.

Arm type	Active comparator
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Investigational medicinal product name	Nab-paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nab-paclitaxel 125 mg/m² immediately followed by gemcitabine 1000 mg/m² were administered on Days 1, 8 and 15 of every 28-day cycle via intravenous infusion.

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

Dosage and administration details:

Nab-paclitaxel 125 mg/m² immediately followed by gemcitabine 1000 mg/m² were administered on Days 1, 8 and 15 of every 28-day cycle via intravenous infusion.

Number of subjects in period 1	Napabucasin plus Nab-paclitaxel with Gemcitabine	Nab-paclitaxel with Gemcitabine
Started	565	569
Completed	464	464
Not completed	101	105
Study Termination	101	105

Baseline characteristics

Reporting groups

Reporting group title	Napabucasin plus Nab-paclitaxel with Gemcitabine
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Reporting group description:

All participants who were randomized to Arm 1 to receive napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.

Reporting group title	Nab-paclitaxel with Gemcitabine
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Reporting group description:

All participants who were randomized to Arm 2 to receive nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.

Reporting group values	Napabucasin plus Nab-paclitaxel with Gemcitabine	Nab-paclitaxel with Gemcitabine	Total
Number of subjects	565	569	1134
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	63.0	64.0	
full range (min-max)	31 to 86	27 to 86	-
Gender categorical Units: Subjects			
Female	240	263	503
Male	325	306	631

End points

End points reporting groups

Reporting group title	Napabucasin plus Nab-paclitaxel with Gemcitabine
Reporting group description: All participants who were randomized to Arm 1 to receive napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.	
Reporting group title	Nab-paclitaxel with Gemcitabine
Reporting group description: All participants who were randomized to Arm 2 to receive nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.	
Subject analysis set title	1 - Response Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who were randomized to Arm1 to receive napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4weeks and had measurable disease per RECIST 1.1 at randomization.	
Subject analysis set title	2 - Response Analysis Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who were randomized to Arm 2 to receive nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks and had measurable disease per RECIST 1.1 at randomization.	
Subject analysis set title	1 - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received at least 1 dose of napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4weeks.	
Subject analysis set title	2 - Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received at least 1 dose of nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.	
Subject analysis set title	1 - QoL
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who were randomized to Arm1 to receive napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks, and had at least one valid assessment at each analysis window.	
Subject analysis set title	2 - QoL
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who were randomized to Arm2 to receive nab-paclitaxel and gemcitabine administered intravenously, once weekly, on3 of every 4 weeks, and had at least one valid assessment at each analysis window.	
Subject analysis set title	1 - pSTAT3 positive
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who were randomized to Arm1 to receive napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4weeks and were assessed to have positivepSTAT3 status based on their biomarker data.	
Subject analysis set title	2 - pSTAT3 positive
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who were randomized to Arm2 to receive nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks and were assessed to have positive pSTAT3 status based on their biomarker data.

Subject analysis set title	1 - pSTAT3 positive; RAS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who were randomized to Arm1 to receive napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks, were assessed to have positive pSTAT3 status based on their biomarker data and had measurable disease per RECIST 1.1 at randomization.

Subject analysis set title	2 - pSTAT3 positive; RAS
Subject analysis set type	Sub-group analysis

Subject analysis set description:

All participants who were randomized to Arm2 to receive nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks, were assessed to have positive pSTAT3 status based on their biomarker data and had measurable disease per RECIST 1.1 at randomization.

Primary: Overall Survival

End point title	Overall Survival
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End point description:

To assess the effect of napabucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine on the Overall Survival of patients with metastatic pancreatic ductal adenocarcinoma.

End point type	Primary
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End point timeframe:

Duration of Study

End point values	Napabucasin plus Nab-paclitaxel with Gemcitabine	Nab-paclitaxel with Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	565	569		
Units: Months				
median (confidence interval 95%)	11.43 (10.51 to 12.19)	11.73 (10.74 to 12.71)		

Statistical analyses

Statistical analysis title	Statistical Test of Hypothesis
Comparison groups	Napabucasin plus Nab-paclitaxel with Gemcitabine v Nab-paclitaxel with Gemcitabine
Number of subjects included in analysis	1134
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8419
Method	Logrank

Secondary: Progression Free Survival

End point title	Progression Free Survival
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End point description:

To assess the effect of napabucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine on the Progression Free Survival (PFS) of patients with metastatic pancreatic ductal adenocarcinoma. PFS is defined as the time from randomization to the first objective documentation of disease progression or death due to any cause.

End point type	Secondary
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End point timeframe:

Duration of Study

End point values	Napabucasin plus Nab-paclitaxel with Gemcitabine	Nab-paclitaxel with Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	565	569		
Units: Months				
median (confidence interval 95%)	6.70 (5.68 to 7.26)	6.08 (5.59 to 7.10)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate
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End point description:

To assess the effect of napabucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine on the Disease Control Rate (DCR) of patients with metastatic pancreatic ductal adenocarcinoma. DCR is defined as the proportion of patients with a documented complete response, partial response, and stable disease (CR + PR + SD) based on RECIST 1.1.

End point type	Secondary
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End point timeframe:

Duration of Study

End point values	1 - Response Analysis Set	2 - Response Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	556	559		
Units: Percentage				
number (confidence interval 95%)	74 (71 to 78)	76 (72 to 80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate
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End point description:

To assess the effect of napabucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine on the Overall Response Rate (ORR) of patients with metastatic pancreatic ductal adenocarcinoma. ORR is evaluated using RECIST 1.1.

End point type	Secondary
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End point timeframe:

Duration of Study

End point values	1 - Response Analysis Set	2 - Response Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	556	559		
Units: Percentage				
number (confidence interval 95%)	43 (39 to 47)	43 (39 to 47)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Adverse Events

End point title	Number of Patients With Adverse Events
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End point description:

All patients who have received at least one dose of napabucasin will be included in the safety analysis according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.0. The incidence of adverse events will be summarized by type of adverse event and severity.

End point type	Secondary
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End point timeframe:

Duration of Study

End point values	1 - Safety Population	2 - Safety Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	561	547		
Units: Participants	560	543		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline for Global Quality of Life (QoL) at 8 Weeks.

End point title	Mean Change From Baseline for Global Quality of Life (QoL) at 8 Weeks.
End point description:	
QoL will be measured using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30) in patients with metastatic pancreatic ductal adenocarcinoma with nababucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine. EORTC QLC-C30 is a questionnaire used to assess the overall quality of life in cancer patients - 28 questions use a 4-point scale (1 'Not at All' to 4 'Very Much'); 2 questions use a 7-point scale (1 'Very Poor' to 7 'Excellent'). Higher overall score = better quality of life.	
End point type	Secondary
End point timeframe:	
8 weeks	

End point values	1 - QoL	2 - QoL		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	420	430		
Units: Score on a scale				
number (not applicable)	-1.63	-0.57		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall Survival in Biomarker Positive Patients

End point title	Overall Survival in Biomarker Positive Patients
End point description:	
To assess the effect of nababucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine on the Overall Survival of patients with metastatic pancreatic ductal adenocarcinoma in biomarker positive patients. This biomarker-positive sub-population is defined as those patients with phospho-STAT3 positivity based on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) tumor tissue.	
End point type	Other pre-specified
End point timeframe:	
Duration of Study	

End point values	1 - pSTAT3 positive	2 - pSTAT3 positive		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	176		
Units: Months				
median (confidence interval 95%)	11.40 (10.02 to 12.42)	10.78 (9.40 to 12.55)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Progression Free Survival in Biomarker Positive Patients

End point title	Progression Free Survival in Biomarker Positive Patients
End point description:	
To assess the effect of napabucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine on the Progression Free Survival (PFS) of patients with metastatic pancreatic ductal adenocarcinoma in biomarker positive patients. PFS is defined as the time from randomization to the first objective documentation of disease progression or death due to any cause. This biomarker-positive sub-population is defined as those patients with phospho-STAT3 positivity based on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) tumor tissue.	
End point type	Other pre-specified
End point timeframe:	
Duration of Study	

End point values	1 - pSTAT3 positive	2 - pSTAT3 positive		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	206	176		
Units: Months				
median (confidence interval 95%)	5.68 (5.49 to 7.39)	5.82 (5.55 to 7.29)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Disease Control Rate in Biomarker Positive Patients

End point title	Disease Control Rate in Biomarker Positive Patients
End point description:	
To assess the effect of napabucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine on the Disease Control Rate (DCR) of patients with metastatic pancreatic ductal adenocarcinoma in biomarker positive patients. DCR is evaluated using RECIST 1.1. This	

biomarker-positive sub-population is defined as those patients with phospho-STAT3 positivity based on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) tumor tissue.

End point type	Other pre-specified
End point timeframe:	
Duration of Study	

End point values	1 - pSTAT3 positive; RAS	2 - pSTAT3 positive; RAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	173		
Units: Percentage				
number (confidence interval 95%)	75 (69 to 81)	79 (72 to 84)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall Response Rate in Biomarker Positive Patients

End point title	Overall Response Rate in Biomarker Positive Patients
End point description:	
To assess the effect of nababucasin plus weekly nab-paclitaxel with gemcitabine versus weekly nab-paclitaxel with gemcitabine on the Overall Response Rate (ORR) of patients with metastatic pancreatic ductal adenocarcinoma in biomarker positive patients. ORR is evaluated using RECIST 1.1. This biomarker-positive sub-population is defined as those patients with phospho-STAT3 positivity based on immunohistochemical (IHC) staining of Formalin Fixed Paraffin Embedded (FFPE) tumor tissue.	
End point type	Other pre-specified
End point timeframe:	
Duration of Study	

End point values	1 - pSTAT3 positive; RAS	2 - pSTAT3 positive; RAS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	203	173		
Units: Months				
number (confidence interval 95%)	42 (35 to 49)	47 (40 to 55)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Duration of Study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Napabucasin plus Nab-paclitaxel with Gemcitabine
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Reporting group description:

All participants who received at least 1 dose of napabucasin administered orally, twice daily in combination with weekly nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.

Reporting group title	Nab-paclitaxel with Gemcitabine
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Reporting group description:

All participants who received at least 1 dose of nab-paclitaxel and gemcitabine administered intravenously, once weekly, on 3 of every 4 weeks.

Serious adverse events	Napabucasin plus Nab-paclitaxel with Gemcitabine	Nab-paclitaxel with Gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	330 / 561 (58.82%)	273 / 547 (49.91%)	
number of deaths (all causes)	419	400	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oncologic complication			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 561 (0.18%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary serous endometrialcarcinoma			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aneurysm ruptured			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Capillary leak syndrome			
subjects affected / exposed	2 / 561 (0.36%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 561 (0.18%)	4 / 547 (0.73%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	4 / 561 (0.71%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 5	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Embolism venous			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 561 (0.36%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	5 / 561 (0.89%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral venous disease			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
Thrombophlebitis			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trousseau's syndrome			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pancreaticoduodenectomy			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 561 (1.78%)	11 / 547 (2.01%)	
occurrences causally related to treatment / all	15 / 17	9 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest discomfort			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	3 / 561 (0.53%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Death			
subjects affected / exposed	3 / 561 (0.53%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Device related thrombosis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	45 / 561 (8.02%)	22 / 547 (4.02%)	
occurrences causally related to treatment / all	1 / 56	1 / 23	
deaths causally related to treatment / all	1 / 37	1 / 15	
Fatigue			

subjects affected / exposed	8 / 561 (1.43%)	5 / 547 (0.91%)	
occurrences causally related to treatment / all	7 / 11	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	7 / 561 (1.25%)	7 / 547 (1.28%)	
occurrences causally related to treatment / all	2 / 8	4 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 561 (0.53%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	34 / 561 (6.06%)	29 / 547 (5.30%)	
occurrences causally related to treatment / all	14 / 36	11 / 33	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	1 / 561 (0.18%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis allergic			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	9 / 561 (1.60%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	1 / 9	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 561 (0.18%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 561 (0.53%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	4 / 561 (0.71%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	5 / 561 (0.89%)	6 / 547 (1.10%)	
occurrences causally related to treatment / all	5 / 6	6 / 6	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pneumothorax			

subjects affected / exposed	3 / 561 (0.53%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	10 / 561 (1.78%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	2 / 10	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 561 (0.53%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Confusional state			
subjects affected / exposed	3 / 561 (0.53%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			

subjects affected / exposed	0 / 561 (0.00%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device extrusion			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	3 / 561 (0.53%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile output increased			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	6 / 561 (1.07%)	5 / 547 (0.91%)	
occurrences causally related to treatment / all	1 / 7	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
General physical condition abnormal			
subjects affected / exposed	1 / 561 (0.18%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
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	3 / 561 (0.53%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	5 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	2 / 561 (0.36%)	4 / 547 (0.73%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 561 (0.18%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	1 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic complication			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical poisoning			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural bile leak			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative hernia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 561 (0.18%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			

Acute coronary syndrome subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (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 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation subjects affected / exposed	4 / 561 (0.71%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure subjects affected / exposed	3 / 561 (0.53%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure congestive subjects affected / exposed	2 / 561 (0.36%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Myocardial infarction			

subjects affected / exposed	2 / 561 (0.36%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Axonal neuropathy			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
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	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebral thrombosis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	4 / 561 (0.71%)	4 / 547 (0.73%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic stroke			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhage intracranial			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbosacral plexopathy			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
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 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Acquired haemophilia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	22 / 561 (3.92%)	12 / 547 (2.19%)	
occurrences causally related to treatment / all	31 / 34	16 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of chronic disease			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 561 (0.18%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	10 / 561 (1.78%)	16 / 547 (2.93%)	
occurrences causally related to treatment / all	11 / 11	16 / 17	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemolytic anaemia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 561 (0.18%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	8 / 561 (1.43%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	8 / 8	4 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancytopenia			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic vein thrombosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	5 / 561 (0.89%)	4 / 547 (0.73%)	
occurrences causally related to treatment / all	18 / 18	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	2 / 561 (0.36%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	2 / 561 (0.36%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	30 / 561 (5.35%)	21 / 547 (3.84%)	
occurrences causally related to treatment / all	8 / 38	1 / 24	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal ulcer			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	4 / 561 (0.71%)	5 / 547 (0.91%)	
occurrences causally related to treatment / all	0 / 6	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	5 / 561 (0.89%)	4 / 547 (0.73%)	
occurrences causally related to treatment / all	4 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	6 / 561 (1.07%)	4 / 547 (0.73%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	23 / 561 (4.10%)	17 / 547 (3.11%)	
occurrences causally related to treatment / all	22 / 24	15 / 20	
deaths causally related to treatment / all	0 / 0	1 / 1	
Diarrhoea haemorrhagic			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			

subjects affected / exposed	3 / 561 (0.53%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric perforation			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 561 (0.36%)	7 / 547 (1.28%)	
occurrences causally related to treatment / all	0 / 2	7 / 12	
deaths causally related to treatment / all	0 / 0	1 / 2	
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	2 / 561 (0.36%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 561 (0.53%)	7 / 547 (1.28%)	
occurrences causally related to treatment / all	0 / 3	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
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	4 / 561 (0.71%)	4 / 547 (0.73%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestinal haemorrhage			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	6 / 561 (1.07%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 8	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestinal ulcer			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	2 / 561 (0.36%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant bowel obstruction			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	21 / 561 (3.74%)	12 / 547 (2.19%)	
occurrences causally related to treatment / all	18 / 24	10 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	3 / 561 (0.53%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic necrosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 561 (0.53%)	5 / 547 (0.91%)	
occurrences causally related to treatment / all	1 / 3	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	4 / 561 (0.71%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	5 / 561 (0.89%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic artery aneurysm			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Truncus coeliacus thrombosis			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 561 (0.53%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	27 / 561 (4.81%)	12 / 547 (2.19%)	
occurrences causally related to treatment / all	18 / 29	9 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	4 / 561 (0.71%)	7 / 547 (1.28%)	
occurrences causally related to treatment / all	0 / 6	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	2 / 561 (0.36%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (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	7 / 561 (1.25%)	15 / 547 (2.74%)	
occurrences causally related to treatment / all	0 / 10	1 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	3 / 561 (0.53%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder perforation			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemobilia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 561 (0.36%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 3	3 / 3	
deaths causally related to treatment / all	0 / 1	1 / 1	
Hepatic haemorrhage			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			

subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	8 / 561 (1.43%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 11	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash erythematous			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 561 (1.43%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	5 / 10	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy toxic			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	4 / 561 (0.71%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	2 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary retention			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 561 (0.00%)	6 / 547 (1.10%)	
occurrences causally related to treatment / all	0 / 0	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 2	
Bone pain			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dupuytren's contracture			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle haemorrhage			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (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	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal infection			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	6 / 561 (1.07%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	11 / 561 (1.96%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 13	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	11 / 561 (1.96%)	7 / 547 (1.28%)	
occurrences causally related to treatment / all	4 / 14	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central nervous system infection			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	3 / 561 (0.53%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	3 / 561 (0.53%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	2 / 561 (0.36%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	4 / 561 (0.71%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	2 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epstein-Barr virus infection			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (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 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic infection			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis viral			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	4 / 561 (0.71%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	1 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	4 / 561 (0.71%)	8 / 547 (1.46%)	
occurrences causally related to treatment / all	1 / 4	2 / 11	
deaths causally related to treatment / all	0 / 0	1 / 1	
Lung infection			
subjects affected / exposed	4 / 561 (0.71%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	2 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic abscess			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perihepatic abscess			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	2 / 561 (0.36%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal cyst			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	14 / 561 (2.50%)	21 / 547 (3.84%)	
occurrences causally related to treatment / all	2 / 15	12 / 28	
deaths causally related to treatment / all	0 / 0	1 / 3	
Pneumonia chlamydial			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate infection			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	2 / 561 (0.36%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal abscess			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	23 / 561 (4.10%)	18 / 547 (3.29%)	
occurrences causally related to treatment / all	9 / 27	7 / 21	
deaths causally related to treatment / all	2 / 5	1 / 3	
Septic shock			
subjects affected / exposed	5 / 561 (0.89%)	5 / 547 (0.91%)	
occurrences causally related to treatment / all	1 / 6	2 / 8	
deaths causally related to treatment / all	1 / 2	1 / 3	
Skin infection			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic abscess			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 561 (0.36%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	10 / 561 (1.78%)	7 / 547 (1.28%)	
occurrences causally related to treatment / all	2 / 12	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral sepsis			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 561 (1.43%)	6 / 547 (1.10%)	
occurrences causally related to treatment / all	6 / 9	2 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dehydration			
subjects affected / exposed	18 / 561 (3.21%)	6 / 547 (1.10%)	
occurrences causally related to treatment / all	21 / 23	3 / 6	
deaths causally related to treatment / all	1 / 1	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
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 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
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	3 / 561 (0.53%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			

subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 561 (0.53%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 561 (0.00%)	3 / 547 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 561 (0.18%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 561 (0.00%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 561 (0.36%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 561 (0.00%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	7 / 561 (1.25%)	1 / 547 (0.18%)	
occurrences causally related to treatment / all	1 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoproteinaemia			

subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 561 (0.18%)	2 / 547 (0.37%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	1 / 561 (0.18%)	0 / 547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Napabucasin plus Nab-paclitaxel with Gemcitabine	Nab-paclitaxel with Gemcitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	560 / 561 (99.82%)	543 / 547 (99.27%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	92 / 561 (16.40%)	93 / 547 (17.00%)	
occurrences (all)	179	212	
Aspartate aminotransferase increased			
subjects affected / exposed	85 / 561 (15.15%)	88 / 547 (16.09%)	
occurrences (all)	142	183	
Blood alkaline phosphatase increased			
subjects affected / exposed	62 / 561 (11.05%)	57 / 547 (10.42%)	
occurrences (all)	110	88	
Blood bilirubin increased			

subjects affected / exposed	48 / 561 (8.56%)	36 / 547 (6.58%)	
occurrences (all)	92	60	
Gamma-glutamyltransferase increased			
subjects affected / exposed	28 / 561 (4.99%)	30 / 547 (5.48%)	
occurrences (all)	63	70	
Neutrophil count decreased			
subjects affected / exposed	138 / 561 (24.60%)	155 / 547 (28.34%)	
occurrences (all)	548	678	
Platelet count decreased			
subjects affected / exposed	111 / 561 (19.79%)	143 / 547 (26.14%)	
occurrences (all)	5	12	
Weight decreased			
subjects affected / exposed	91 / 561 (16.22%)	69 / 547 (12.61%)	
occurrences (all)	136	95	
White blood cell count decreased			
subjects affected / exposed	120 / 561 (21.39%)	137 / 547 (25.05%)	
occurrences (all)	542	561	
Nervous system disorders			
Dizziness			
subjects affected / exposed	52 / 561 (9.27%)	51 / 547 (9.32%)	
occurrences (all)	78	68	
Dysgeusia			
subjects affected / exposed	82 / 561 (14.62%)	84 / 547 (15.36%)	
occurrences (all)	94	99	
Headache			
subjects affected / exposed	49 / 561 (8.73%)	43 / 547 (7.86%)	
occurrences (all)	67	55	
Neuropathy peripheral			
subjects affected / exposed	125 / 561 (22.28%)	133 / 547 (24.31%)	
occurrences (all)	244	282	
Paraesthesia			
subjects affected / exposed	24 / 561 (4.28%)	29 / 547 (5.30%)	
occurrences (all)	46	65	
Peripheral sensory neuropathy			

subjects affected / exposed occurrences (all)	92 / 561 (16.40%) 158	97 / 547 (17.73%) 185	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	306 / 561 (54.55%)	318 / 547 (58.14%)	
occurrences (all)	1243	1295	
Leukopenia			
subjects affected / exposed	56 / 561 (9.98%)	56 / 547 (10.24%)	
occurrences (all)	191	176	
Neutropenia			
subjects affected / exposed	145 / 561 (25.85%)	165 / 547 (30.16%)	
occurrences (all)	452	582	
Thrombocytopenia			
subjects affected / exposed	105 / 561 (18.72%)	126 / 547 (23.03%)	
occurrences (all)	352	425	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	143 / 561 (25.49%)	137 / 547 (25.05%)	
occurrences (all)	332	385	
Chills			
subjects affected / exposed	28 / 561 (4.99%)	16 / 547 (2.93%)	
occurrences (all)	30	19	
Disease progression			
subjects affected / exposed	45 / 561 (8.02%)	23 / 547 (4.20%)	
occurrences (all)	58	25	
Fatigue			
subjects affected / exposed	205 / 561 (36.54%)	189 / 547 (34.55%)	
occurrences (all)	508	415	
Malaise			
subjects affected / exposed	48 / 561 (8.56%)	30 / 547 (5.48%)	
occurrences (all)	98	56	
Oedema peripheral			
subjects affected / exposed	179 / 561 (31.91%)	180 / 547 (32.91%)	
occurrences (all)	323	322	
Pain			

subjects affected / exposed	33 / 561 (5.88%)	34 / 547 (6.22%)	
occurrences (all)	57	58	
Pyrexia			
subjects affected / exposed	211 / 561 (37.61%)	203 / 547 (37.11%)	
occurrences (all)	526	527	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	44 / 561 (7.84%)	32 / 547 (5.85%)	
occurrences (all)	64	41	
Abdominal pain			
subjects affected / exposed	215 / 561 (38.32%)	124 / 547 (22.67%)	
occurrences (all)	416	214	
Abdominal pain upper			
subjects affected / exposed	70 / 561 (12.48%)	46 / 547 (8.41%)	
occurrences (all)	94	68	
Ascites			
subjects affected / exposed	29 / 561 (5.17%)	31 / 547 (5.67%)	
occurrences (all)	54	44	
Constipation			
subjects affected / exposed	194 / 561 (34.58%)	209 / 547 (38.21%)	
occurrences (all)	263	323	
Diarrhoea			
subjects affected / exposed	410 / 561 (73.08%)	213 / 547 (38.94%)	
occurrences (all)	1082	440	
Dyspepsia			
subjects affected / exposed	47 / 561 (8.38%)	34 / 547 (6.22%)	
occurrences (all)	57	45	
Nausea			
subjects affected / exposed	329 / 561 (58.65%)	252 / 547 (46.07%)	
occurrences (all)	681	545	
Stomatitis			
subjects affected / exposed	39 / 561 (6.95%)	52 / 547 (9.51%)	
occurrences (all)	53	83	
Vomiting			
subjects affected / exposed	250 / 561 (44.56%)	162 / 547 (29.62%)	
occurrences (all)	578	305	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	68 / 561 (12.12%)	74 / 547 (13.53%)	
occurrences (all)	93	92	
Dyspnoea			
subjects affected / exposed	69 / 561 (12.30%)	69 / 547 (12.61%)	
occurrences (all)	109	107	
Epistaxis			
subjects affected / exposed	52 / 561 (9.27%)	55 / 547 (10.05%)	
occurrences (all)	60	62	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	212 / 561 (37.79%)	210 / 547 (38.39%)	
occurrences (all)	257	261	
Pruritus			
subjects affected / exposed	48 / 561 (8.56%)	51 / 547 (9.32%)	
occurrences (all)	58	64	
Rash			
subjects affected / exposed	89 / 561 (15.86%)	85 / 547 (15.54%)	
occurrences (all)	129	136	
Rash maculo-papular			
subjects affected / exposed	29 / 561 (5.17%)	32 / 547 (5.85%)	
occurrences (all)	45	37	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	38 / 561 (6.77%)	28 / 547 (5.12%)	
occurrences (all)	39	32	
Insomnia			
subjects affected / exposed	62 / 561 (11.05%)	70 / 547 (12.80%)	
occurrences (all)	70	78	
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	50 / 561 (8.91%)	7 / 547 (1.28%)	
occurrences (all)	52	7	
Hypertension			

subjects affected / exposed	40 / 561 (7.13%)	52 / 547 (9.51%)	
occurrences (all)	98	118	
Hypotension			
subjects affected / exposed	23 / 561 (4.10%)	28 / 547 (5.12%)	
occurrences (all)	24	37	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	29 / 561 (5.17%)	51 / 547 (9.32%)	
occurrences (all)	39	71	
Back pain			
subjects affected / exposed	68 / 561 (12.12%)	65 / 547 (11.88%)	
occurrences (all)	93	99	
Muscular weakness			
subjects affected / exposed	30 / 561 (5.35%)	21 / 547 (3.84%)	
occurrences (all)	38	29	
Myalgia			
subjects affected / exposed	41 / 561 (7.31%)	44 / 547 (8.04%)	
occurrences (all)	49	61	
Pain in extremity			
subjects affected / exposed	43 / 561 (7.66%)	39 / 547 (7.13%)	
occurrences (all)	58	54	
Infections and infestations			
Pneumonia			
subjects affected / exposed	31 / 561 (5.53%)	33 / 547 (6.03%)	
occurrences (all)	39	50	
Upper respiratory tract infection			
subjects affected / exposed	41 / 561 (7.31%)	35 / 547 (6.40%)	
occurrences (all)	47	44	
Urinary tract infection			
subjects affected / exposed	64 / 561 (11.41%)	41 / 547 (7.50%)	
occurrences (all)	91	53	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	233 / 561 (41.53%)	177 / 547 (32.36%)	
occurrences (all)	406	312	
Dehydration			

subjects affected / exposed	61 / 561 (10.87%)	37 / 547 (6.76%)	
occurrences (all)	78	46	
Hyperglycaemia			
subjects affected / exposed	28 / 561 (4.99%)	30 / 547 (5.48%)	
occurrences (all)	36	60	
Hypoalbuminaemia			
subjects affected / exposed	76 / 561 (13.55%)	74 / 547 (13.53%)	
occurrences (all)	171	146	
Hypokalaemia			
subjects affected / exposed	65 / 561 (11.59%)	55 / 547 (10.05%)	
occurrences (all)	117	105	
Hyponatraemia			
subjects affected / exposed	56 / 561 (9.98%)	26 / 547 (4.75%)	
occurrences (all)	105	45	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2017	The protocol was amended to reflect requests from various Regulatory Authorities, update the inclusion/exclusion criteria, correct errors and inconsistencies, and include clarifications.
16 February 2018	The protocol was amended for consistency with the most recent edition of the napabucasin Investigator's Brochure, to remove the efficacy analysis from the first interim analysis while keeping the futility analysis, to clarify sensitivity and subgroup analysis for overall survival, to remove the multiplicity adjustment for the secondary endpoints, to clarify the one-sided futility and efficacy boundaries for the interim analyses and the final analysis, to correct transcription errors, and to include other clarifications.
04 December 2018	The protocol was amended to update the study objectives, reflect the addition of multiplicity adjustment strategy, include information on the Sponsor's blinding plan, correct transcription errors, reflect the Sponsor's updated practices for AE reporting, and provide clarifications.
31 July 2019	The protocol was amended to reflect the outcome of the interim analysis, the DSMB recommendation and the plan to complete the study on February 28th, 2020.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported