

**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:

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**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
<b>Arm title</b>	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/m<sup>2</sup> immediately followed by gemcitabine 1000 mg/m<sup>2</sup> 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/m<sup>2</sup> immediately followed by gemcitabine 1000 mg/m<sup>2</sup> were administered on Days 1, 8 and 15 of every 28-day cycle via intravenous infusion.

<b>Arm title</b>	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/m<sup>2</sup> immediately followed by gemcitabine 1000 mg/m<sup>2</sup> 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/m<sup>2</sup> immediately followed by gemcitabine 1000 mg/m<sup>2</sup> were administered on Days 1, 8 and 15 of every 28-day cycle via intravenous infusion.

<b>Number of subjects in period 1</b>	Napabucasin plus Nab-paclitaxel with Gemcitabine	Nab-paclitaxel with Gemcitabine
	Started	565
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 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 nab-paclitaxel 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

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**Secondary: Progression Free Survival**

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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

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<b>End point values</b>	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)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Disease Control Rate**

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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

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<b>End point values</b>	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

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

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

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

End point timeframe:

Duration of Study

<b>End point values</b>	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.
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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
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End point timeframe:

8 weeks

<b>End point values</b>	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
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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
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End point timeframe:

Duration of Study

<b>End point values</b>	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
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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 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
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End point timeframe:

Duration of Study

<b>End point values</b>	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
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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 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
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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
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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
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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.

<b>Serious adverse events</b>	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	
<b>General disorders and administration site conditions</b>			
<b>Asthenia</b>			
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	
<b>Chest discomfort</b>			
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	
<b>Chest pain</b>			
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	
<b>Condition aggravated</b>			
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	
<b>Death</b>			
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	
<b>Device related thrombosis</b>			
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	
<b>Disease progression</b>			
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	
<b>Fatigue</b>			

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	
<b>Pulmonary embolism</b>			
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	
<b>Pulmonary hypertension</b>			
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	
<b>Pulmonary oedema</b>			
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	
<b>Respiratory failure</b>			
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	
<b>Psychiatric disorders</b>			
<b>Anxiety</b>			
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	
<b>Completed suicide</b>			
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	
<b>Confusional state</b>			
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	
<b>Depression</b>			

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	
<b>Palpitations</b>			
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	
<b>Sinus tachycardia</b>			
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	
<b>Supraventricular tachycardia</b>			
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	
<b>Nervous system disorders</b>			
<b>Axonal neuropathy</b>			
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	
<b>Cerebral infarction</b>			
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	
<b>Cerebral thrombosis</b>			
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	
<b>Cerebrovascular accident</b>			
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	
<b>Cognitive disorder</b>			

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	
<b>Blood and lymphatic system disorders</b>			
<b>Acquired haemophilia</b>			
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	
<b>Anaemia</b>			
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	
<b>Anaemia of chronic disease</b>			
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	
<b>Bone marrow failure</b>			
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	
<b>Febrile neutropenia</b>			
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	
<b>Haemolytic anaemia</b>			
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	
<b>Haemolytic uraemic syndrome</b>			
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	
<b>Leukocytosis</b>			

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	
<b>Leukopenia</b>			
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	
<b>Neutropenia</b>			
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	
<b>Pancytopenia</b>			
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	
<b>Splenic infarction</b>			
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	
<b>Splenic vein thrombosis</b>			
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	
<b>Thrombocytopenia</b>			
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	
<b>Thrombotic microangiopathy</b>			
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	
<b>Ear and labyrinth disorders</b>			
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
<b>Dysphagia</b>		
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
<b>Enteritis</b>		
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
<b>Enterocolitis</b>		
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
<b>Faecaloma</b>		
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
<b>Gastric haemorrhage</b>		
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
<b>Gastric perforation</b>		
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
<b>Gastric ulcer</b>		
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
<b>Gastritis</b>		

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	
<b>Gastrointestinal disorder</b>			
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	
<b>Gastrointestinal haemorrhage</b>			
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	
<b>Gastrointestinal hypomotility</b>			
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	
<b>Gastrointestinal inflammation</b>			
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	
<b>Gastrointestinal obstruction</b>			
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	
<b>Gastrointestinal pain</b>			
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	
<b>Gastrointestinal toxicity</b>			
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	
<b>Haematemesis</b>			

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
<b>Haematochezia</b>		
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
<b>Ileus</b>		
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
<b>Ileus paralytic</b>		
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
<b>Inguinal hernia</b>		
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
<b>Intestinal obstruction</b>		
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
<b>Intestinal perforation</b>		
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
<b>Intra-abdominal haemorrhage</b>		
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
<b>Large intestinal haemorrhage</b>		

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
<b>Mesenteric vein thrombosis</b>		
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
<b>Nausea</b>		
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
<b>Neutropenic colitis</b>		
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
<b>Obstruction gastric</b>		
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
<b>Pancreatic necrosis</b>		
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
<b>Pancreatitis</b>		
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
<b>Pancreatitis acute</b>		
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
<b>Pneumatosis intestinalis</b>		

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	
<b>Cholecystitis acute</b>			
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	
<b>Cholestasis</b>			
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	
<b>Gallbladder perforation</b>			
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	
<b>Haemobilia</b>			
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	
<b>Hepatic failure</b>			
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	
<b>Hepatic haemorrhage</b>			
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	
<b>Hepatitis acute</b>			
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	
<b>Hyperbilirubinaemia</b>			

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	
<b>Jaundice</b>			
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	
<b>Jaundice cholestatic</b>			
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	
<b>Portal vein thrombosis</b>			
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	
<b>Skin and subcutaneous tissue disorders</b>			
<b>Dermatitis</b>			
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	
<b>Rash erythematous</b>			
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	
<b>Renal and urinary disorders</b>			
<b>Acute kidney injury</b>			
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	
<b>Nephropathy toxic</b>			
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	
<b>Nephrotic syndrome</b>			

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	
<b>Renal failure</b>			
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	
<b>Urinary retention</b>			
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	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Back pain</b>			
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	
<b>Bone pain</b>			
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	
<b>Dupuytren's contracture</b>			
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	
<b>Muscle haemorrhage</b>			
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	
<b>Muscular weakness</b>			
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	
<b>Pain in extremity</b>			

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
<b>Biliary sepsis</b>		
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
<b>Biliary tract infection</b>		
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
<b>Bronchopulmonary aspergillosis</b>		
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
<b>Cellulitis</b>		
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
<b>Central nervous system infection</b>		
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
<b>Clostridium difficile colitis</b>		
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
<b>Clostridium difficile infection</b>		
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
<b>Device related infection</b>		

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
<b>Pyelonephritis</b>		
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
<b>Respiratory tract infection</b>		
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
<b>Retroperitoneal abscess</b>		
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
<b>Rhinovirus infection</b>		
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
<b>Sepsis</b>		
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
<b>Septic shock</b>		
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
<b>Skin infection</b>		
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
<b>Splenic abscess</b>		

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	
<b>Streptococcal sepsis</b>			
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	
<b>Subcutaneous abscess</b>			
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	
<b>Upper respiratory tract infection</b>			
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	
<b>Urinary tract infection</b>			
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	
<b>Urosepsis</b>			
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	
<b>Viral infection</b>			
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	
<b>Viral sepsis</b>			
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	
<b>Viral upper respiratory tract infection</b>			

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
<b>Hyperglycaemia</b>		
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
<b>Hyperkalaemia</b>		
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
<b>Hypoalbuminaemia</b>		
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
<b>Hypoglycaemia</b>		
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
<b>Hypokalaemia</b>		
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
<b>Hypomagnesaemia</b>		
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
<b>Hyponatraemia</b>		
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
<b>Hypoproteinaemia</b>		

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	
<b>Hypovolaemia</b>			
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	
<b>Malnutrition</b>			
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	
<b>Metabolic acidosis</b>			
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 %

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

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

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

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported