Clinical trial results:
A Phase III Open-Label, Multi-Centre, Randomised Study Comparing NUC-1031 plus Cisplatin to Gemcitabine plus Cisplatin in Patients with Previously Untreated Locally Advanced or Metastatic Biliary Tract Cancer

Summary

EudraCT number	2019-001025-28
Trial protocol	GB FR HU ES DE IT
Global end of trial date	05 April 2022

Results information

Result version number	v1 (current)
This version publication date	19 March 2023
First version publication date	19 March 2023

Trial information

Trial identification

Sponsor protocol code	NuTide:121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04163900
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	NuCana plc
Sponsor organisation address	3 Lochside Way, Edinburgh, United Kingdom, EH12 9DT
Public contact	NuCana Clinical Study Information, NuCana plc, +44 1313571111, info@nucana.com
Scientific contact	NuCana Clinical Study Information, NuCana plc, +44 1313571111, info@nucana.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	05 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 April 2022
Global end of trial reached?	Yes
Global end of trial date	05 April 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To compare NUC-1031 + cisplatin (Arm A) to the gemcitabine + cisplatin standard of care (Arm B) and to detect a clinically meaningful improvement in Overall Survival (OS) and Objective Response Rate (ORR).
At Interim Analysis 1, the IDMC concluded that NUC-1031 + cisplatin was unlikely to achieve the first primary objective of obtaining statistical significance for OS compared to gemcitabine + cisplatin. The study was stopped for futility on 02 Mar 2022.

Protection of trial subjects:

The Chief Investigator (CI) ensured that the study was conducted in full conformity with the principles of the 1964 Declaration of Helsinki and any subsequent revisions and in accordance with the guidelines laid down by the International Conference on Harmonisation for Good Clinical Practice (ICH GCP E6 guidelines). Precautions were taken to ensure that patient confidentiality was preserved at all times. The Informed Consent Form identified those individuals who required access to patient data and identifiable details and obtained appropriate permission from the consenting patient. The Independent Data Monitoring Committee provided overall supervision of the study and ensured that it was being conducted in accordance with the principles of GCP and the relevant regulations. It provided advice on all aspects of the study as and when necessary.

Background therapy: -

Evidence for comparator:

Although not approved for the treatment of BTC, the combination of gemcitabine and cisplatin is empirically accepted on the basis of clinical studies as the preferred regimen for first-line treatment of patients with BTC. The Phase III ABC-02 study established the combination as the standard of care in this disease (Valle et al, 2016). Furthermore, the combination of gemcitabine and cisplatin is recognised by the National Comprehensive Cancer Network (NCCN) as a Category 1 recommendation for the first-line treatment of patients with BTC (NCCN, 2019). There have been three randomised studies evaluating clinical activity of the combination of gemcitabine and cisplatin in the first-line setting, with dosing on Days 1 and 8, every 21 days (Valle et al, 2010; Okusaka et al, 2010; Valle et al, 2015). The reported ORR (based on unconfirmed responses) from these studies ranged from 18.5 to 26.1%. The median OS across the three studies was remarkably consistent, ranging from 11.2 to 11.9 months.

Actual start date of recruitment	23 December 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	United Kingdom: 85
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 9

Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Australia: 51
Country: Number of subjects enrolled	Canada: 63
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Korea, Republic of: 88
Country: Number of subjects enrolled	Russian Federation: 76
Country: Number of subjects enrolled	Turkey: 20
Country: Number of subjects enrolled	Taiwan: 44
Country: Number of subjects enrolled	Ukraine: 72
Country: Number of subjects enrolled	United States: 127
Worldwide total number of subjects	773
EEA total number of subjects	232

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	371
From 65 to 84 years	396
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

A total of 1031 patients were screened, of whom 773 patients were randomised and 761 received at least one dose of study treatment.

Pre-assignment

Screening details:

Patients with histologically- or cytologically-proven biliary adenocarcinoma, including cholangiocarcinoma (intra- and extra hepatic biliary ducts), gallbladder or ampullary cancer, that was not amenable to surgical resection and who had no prior systemic chemotherapy for treatment of locally advanced or metastatic disease were eligible.

Period 1

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

Blinding implementation details:

This study was not blinded. However, primary analyses of objective response data used BICR assessment of radiologic evaluation using blinded double reads with adjudication.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

NUC-1031 + cisplatin

Arm type	Experimental
Investigational medicinal product name	fosgemcitabine palabenamide
Investigational medicinal product code	NUC-1031
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

NUC-1031 725 mg/m2 on Days 1 and 8 of 21-day cycles

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

Dosage and administration details:

Cisplatin 25 mg/m2 on Days 1 and 8 of 21-day cycles

Arm title	Arm B

Arm description:

Gemcitabine + cisplatin

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

Dosage and administration details: Gemcitabine 1000 mg/m2 on Days 1 and 8 of 21-day cycles	
Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cisplatin 25 mg/m2 on Days 1 and 8 of 21-day cycles

Number of subjects in period 1	Arm A	Arm B
Started	388	385
Completed	0	0
Not completed	388	385
Clinical progression	14	13
Consent withdrawn by subject	37	34
Physician decision	17	25
Adverse event, non-fatal	78	32
Death	29	16
Progressive disease	112	127
Lost to follow-up	-	1
Protocol deviation	3	4
Study closure	98	133

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description: NUC-1031 + cisplatin	
Reporting group title	Arm B
Reporting group description: Gemcitabine + cisplatin	

Reporting group values	Arm A	Arm B	Total
Number of subjects	388	385	773
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	185	186	371
From 65-84 years	200	196	396
85 years and over	3	3	6
Age continuous Units: years			
median	65.0	65.0	
full range (min-max)	31 to 87	20 to 86	-
Gender categorical Units: Subjects			
Female	174	188	362
Male	214	197	411
Ethnicity Units: Subjects			
Hispanic or Latino	21	31	52
Not Hispanic or Latino	359	337	696
Unknown or Not Reported	8	17	25
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	76	77	153
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	3	5	8
White	285	274	559
Unknown or Not Reported	23	28	51
Primary Tumour Location Units: Subjects			
Gallbladder	80	80	160

Intra-hepatic	209	207	416
Extra-hepatic	80	80	160
Ampullary	19	18	37
Extent of Disease Units: Subjects			
Locally Advanced	56	65	121
Metastatic	330	320	650
Unknown	2	0	2
Measurable Disease Units: Subjects			
Yes	367	366	733
No	21	19	40
ECOG Performance Status Units: Subjects			
Zero	205	186	391
One	178	192	370
Unknown	5	7	12

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description: NUC-1031 + cisplatin	
Reporting group title	Arm B
Reporting group description: Gemcitabine + cisplatin	

Primary: Overall Survival

End point title	Overall Survival[1]
End point description: The median time, in months, from the date of randomization to the date of death from any cause	
End point type	Primary
End point timeframe: Evaluated on an ongoing basis from randomization, then every 12 weeks from the date of treatment discontinuation until the date of death from any cause, up to a maximum of 18 months after the last patient starts treatment	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was stopped early for futility; therefore, the analyses performed should only be viewed descriptively.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	388	385		
Units: Months				
median (confidence interval 95%)	9.2 (8.3 to 10.4)	12.6 (11.0 to 15.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Objective Response Rate

End point title	Objective Response Rate[2]
End point description: Percentage of patients achieving a confirmed complete or partial response to treatment as assessed by blinded independent central review according to RECIST v1.1 criteria in patients with measurable disease at baseline. Patients were to receive a confirmatory scan 28-42 days after response is first observed.	
End point type	Primary
End point timeframe: Evaluated every 9 weeks from start of treatment or, where treatment is stopped with no evidence of progression, every 12 weeks until disease progression or death from any cause, up to a maximum of 18 months after the last patient starts treatment.	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The study was stopped early for futility; therefore, the analyses performed should only be viewed descriptively.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	275		
Units: Percentage	19	12		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Date of consent until 30 days after the last dose of study treatment, up to end of the study (approximately 2 years, 3 months)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	Arm A
Reporting group description: NUC-1031 + cisplatin	
Reporting group title	Arm B
Reporting group description: Gemcitabine + cisplatin	

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	175 / 383 (45.69%)	126 / 378 (33.33%)	
number of deaths (all causes)	184	132	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
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	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			

subjects affected / exposed	7 / 383 (1.83%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	4 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	2 / 383 (0.52%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Embolism arterial			
subjects affected / exposed	1 / 383 (0.26%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
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 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 383 (0.52%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	1 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			

subjects affected / exposed	2 / 383 (0.52%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Discomfort			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	5 / 383 (1.31%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	4 / 383 (1.04%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Generalised oedema			
subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Malaise			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			

subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	4 / 383 (1.04%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	4 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	12 / 383 (3.13%)	18 / 378 (4.76%)	
occurrences causally related to treatment / all	1 / 12	10 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 383 (0.52%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Haemoptysis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	12 / 383 (3.13%)	7 / 378 (1.85%)	
occurrences causally related to treatment / all	4 / 12	2 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Personality change			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 383 (0.52%)	5 / 378 (1.32%)	
occurrences causally related to treatment / all	2 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			

subjects affected / exposed	4 / 383 (1.04%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	4 / 4	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose increased			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple injuries			

subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripancreatic fluid collection			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (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	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site thrombosis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 383 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Angina pectoris			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			

subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 383 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodal arrhythmia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachyarrhythmia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			

subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	3 / 383 (0.78%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	1 / 1	1 / 1	
Encephalopathy			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 383 (0.26%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Seizure			

subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 383 (0.52%)	5 / 378 (1.32%)	
occurrences causally related to treatment / all	2 / 2	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytopenia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	8 / 383 (2.09%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	9 / 9	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (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 distension			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	5 / 383 (1.31%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal rigidity			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	7 / 383 (1.83%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	2 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 383 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			

subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 383 (0.78%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jejunal ulcer			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 383 (0.78%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			

subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 383 (0.78%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vomiting			
subjects affected / exposed	5 / 383 (1.31%)	9 / 378 (2.38%)	
occurrences causally related to treatment / all	3 / 5	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	5 / 383 (1.31%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	8 / 383 (2.09%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	1 / 11	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis acute			
subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis sclerosing			

subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	3 / 383 (0.78%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder rupture			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	5 / 383 (1.31%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	3 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic function abnormal			

subjects affected / exposed	3 / 383 (0.78%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vein embolism			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal failure			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	3 / 383 (0.78%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	3 / 383 (0.78%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	4 / 383 (1.04%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver injury			

subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Portal vein embolism			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 383 (0.52%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 383 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 383 (0.78%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle fatigue			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Muscular weakness			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacillus bacteraemia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (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	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	5 / 383 (1.31%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	2 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Biliary tract infection			

subjects affected / exposed	3 / 383 (0.78%)	5 / 378 (1.32%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	4 / 383 (1.04%)	4 / 378 (1.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	0 / 383 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium bacteraemia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device-related bacteraemia			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 383 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			

subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder abscess			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis B reactivation			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			

subjects affected / exposed	2 / 383 (0.52%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 383 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 383 (0.00%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 383 (0.26%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonsillar abscess			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			

subjects affected / exposed	1 / 383 (0.26%)	2 / 378 (0.53%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	12 / 383 (3.13%)	12 / 378 (3.17%)	
occurrences causally related to treatment / all	4 / 14	2 / 12	
deaths causally related to treatment / all	2 / 3	1 / 1	
Septic shock			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Spontaneous bacterial peritonitis			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdiaphragmatic abscess			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected COVID-19			

subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 383 (1.04%)	3 / 378 (0.79%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 383 (1.31%)	5 / 378 (1.32%)	
occurrences causally related to treatment / all	2 / 6	1 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			

subjects affected / exposed	2 / 383 (0.52%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	4 / 383 (1.04%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 383 (0.26%)	0 / 378 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 383 (0.26%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steroid diabetes			
subjects affected / exposed	0 / 383 (0.00%)	1 / 378 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	370 / 383 (96.61%)	369 / 378 (97.62%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	18 / 383 (4.70%)	13 / 378 (3.44%)	
occurrences (all)	21	16	
Hypertension			
subjects affected / exposed	19 / 383 (4.96%)	26 / 378 (6.88%)	
occurrences (all)	46	73	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	64 / 383 (16.71%)	63 / 378 (16.67%)	
occurrences (all)	121	160	
Oedema peripheral			
subjects affected / exposed	61 / 383 (15.93%)	52 / 378 (13.76%)	
occurrences (all)	110	78	
Fatigue			
subjects affected / exposed	139 / 383 (36.29%)	114 / 378 (30.16%)	
occurrences (all)	278	298	
Pyrexia			
subjects affected / exposed	37 / 383 (9.66%)	45 / 378 (11.90%)	
occurrences (all)	64	82	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	34 / 383 (8.88%)	32 / 378 (8.47%)	
occurrences (all)	50	53	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	19 / 383 (4.96%)	32 / 378 (8.47%)	
occurrences (all)	23	37	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	142 / 383 (37.08%)	62 / 378 (16.40%)	
occurrences (all)	312	131	
Aspartate aminotransferase increased			

subjects affected / exposed	121 / 383 (31.59%)	57 / 378 (15.08%)	
occurrences (all)	228	112	
Blood alkaline phosphatase increased			
subjects affected / exposed	36 / 383 (9.40%)	26 / 378 (6.88%)	
occurrences (all)	67	48	
Blood bilirubin increased			
subjects affected / exposed	66 / 383 (17.23%)	17 / 378 (4.50%)	
occurrences (all)	135	42	
Neutrophil count decreased			
subjects affected / exposed	57 / 383 (14.88%)	83 / 378 (21.96%)	
occurrences (all)	149	232	
Platelet count decreased			
subjects affected / exposed	67 / 383 (17.49%)	63 / 378 (16.67%)	
occurrences (all)	195	247	
White blood cell count decreased			
subjects affected / exposed	25 / 383 (6.53%)	33 / 378 (8.73%)	
occurrences (all)	100	116	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	19 / 383 (4.96%)	2 / 378 (0.53%)	
occurrences (all)	23	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	37 / 383 (9.66%)	27 / 378 (7.14%)	
occurrences (all)	44	30	
Dysgeusia			
subjects affected / exposed	25 / 383 (6.53%)	24 / 378 (6.35%)	
occurrences (all)	29	28	
Headache			
subjects affected / exposed	30 / 383 (7.83%)	29 / 378 (7.67%)	
occurrences (all)	38	39	
Neuropathy peripheral			
subjects affected / exposed	9 / 383 (2.35%)	24 / 378 (6.35%)	
occurrences (all)	12	34	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	99 / 383 (25.85%)	183 / 378 (48.41%)	
occurrences (all)	279	498	
Leukopenia			
subjects affected / exposed	23 / 383 (6.01%)	40 / 378 (10.58%)	
occurrences (all)	44	132	
Neutropenia			
subjects affected / exposed	88 / 383 (22.98%)	133 / 378 (35.19%)	
occurrences (all)	244	364	
Thrombocytopenia			
subjects affected / exposed	76 / 383 (19.84%)	74 / 378 (19.58%)	
occurrences (all)	225	214	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	22 / 383 (5.74%)	14 / 378 (3.70%)	
occurrences (all)	28	22	
Abdominal pain			
subjects affected / exposed	53 / 383 (13.84%)	52 / 378 (13.76%)	
occurrences (all)	113	135	
Abdominal pain upper			
subjects affected / exposed	19 / 383 (4.96%)	36 / 378 (9.52%)	
occurrences (all)	27	47	
Ascites			
subjects affected / exposed	32 / 383 (8.36%)	13 / 378 (3.44%)	
occurrences (all)	56	28	
Constipation			
subjects affected / exposed	105 / 383 (27.42%)	102 / 378 (26.98%)	
occurrences (all)	142	141	
Diarrhoea			
subjects affected / exposed	48 / 383 (12.53%)	56 / 378 (14.81%)	
occurrences (all)	70	86	
Dyspepsia			
subjects affected / exposed	21 / 383 (5.48%)	20 / 378 (5.29%)	
occurrences (all)	25	26	
Nausea			

subjects affected / exposed	167 / 383 (43.60%)	142 / 378 (37.57%)	
occurrences (all)	284	308	
Vomiting			
subjects affected / exposed	81 / 383 (21.15%)	65 / 378 (17.20%)	
occurrences (all)	125	128	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	31 / 383 (8.09%)	8 / 378 (2.12%)	
occurrences (all)	56	19	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	22 / 383 (5.74%)	26 / 378 (6.88%)	
occurrences (all)	23	26	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	39 / 383 (10.18%)	27 / 378 (7.14%)	
occurrences (all)	49	39	
Infections and infestations			
COVID-19			
subjects affected / exposed	20 / 383 (5.22%)	17 / 378 (4.50%)	
occurrences (all)	21	17	
Metabolism and nutrition disorders			
Blood creatine increased			
subjects affected / exposed	9 / 383 (2.35%)	24 / 378 (6.35%)	
occurrences (all)	21	45	
Decreased appetite			
subjects affected / exposed	59 / 383 (15.40%)	55 / 378 (14.55%)	
occurrences (all)	81	83	
Hyperglycaemia			
subjects affected / exposed	22 / 383 (5.74%)	20 / 378 (5.29%)	
occurrences (all)	36	38	
Hypoalbuminaemia			
subjects affected / exposed	39 / 383 (10.18%)	22 / 378 (5.82%)	
occurrences (all)	105	49	
Hypokalaemia			

subjects affected / exposed	27 / 383 (7.05%)	21 / 378 (5.56%)	
occurrences (all)	54	44	
Hypomagnesaemia			
subjects affected / exposed	64 / 383 (16.71%)	59 / 378 (15.61%)	
occurrences (all)	120	114	
Weight decreased			
subjects affected / exposed	20 / 383 (5.22%)	25 / 378 (6.61%)	
occurrences (all)	30	36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 October 2019	• Renal function eligibility criterion updated to allow for a population PK analysis of the effect of renal impairment on the PK of NUC-1031. • Exclusion criterion added to ensure that patients with serious immunodeficiency were not enrolled. • Frequency of pregnancy testing increased to comply with Clinical Trials Facilitation Group guidelines. • Wording updated to reflect that cisplatin should be administered in accordance with local practice. • Criteria for continuation of treatment and dose adjustments revised to comply with an updated Summary of Product Characteristics for gemcitabine. • Description of the PFS analyses updated. • Description of futility boundary updated.
18 December 2020	• Inclusion criterion 8 updated to loosen the required baseline level of haemoglobin from 10 g/dL to 9 g/dL to ensure that otherwise eligible patients were not needlessly excluded. • Exclusion criterion 3 updated to ensure that patients with risk of hypersensitivity to any of the excipients were excluded. • Exclusion criterion 5 updated to allow inclusion of patients with surgically excised or potentially curatively treated ductal carcinoma in situ of the breast, as well as patients who have undergone prior prostatectomy. In addition, this criterion has been amended to allow patients with previous invasive cancers if treatment was completed more than 3 years prior to initiating the current study treatment, and the patient has had no evidence or recurrence since then. • Wording updated to allow patients who initially do not meet certain inclusion/exclusion criteria to be reassessed as needed during the 21-day screening period. • Clarification of the guidelines for patients meeting Hy's law criteria in accordance with FDA guidance. • Clarification to ensure that SAEs were reported from the date of consent through 30 days after the last dose of study drug. • Update to statistical methodology for the secondary and supportive analyses for OS to introduce a censoring-not-at-random approach to assess the robustness of the inference of superiority of the study treatment. • New section added to provide details of additional sensitivity analyses that were to be performed to assess any impact of the COVID-19 pandemic on OS. • Wording added to inform that monitoring may be performed remotely during the COVID 19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

At IA1, the futility boundary for OS was crossed and the study was closed. Analyses performed on the final database were those scheduled to occur at IA2. However, p-values or CIs are only viewed as descriptive as the study was stopped for futility.

Notes: