



Clinical trial results:

An open-label, randomised, multicentre, phase III study of irinotecan liposome injection, oxaliplatin, 5-fluorouracil/leucovorin versus nab-paclitaxel plus gemcitabine in subjects who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas

Summary

EudraCT number	2018-003585-14
Trial protocol	DE ES GB HU BE CZ AT FR PT GR IT
Global end of trial date	

Results information

Result version number	v1
This version publication date	06 April 2024
First version publication date	06 April 2024

Trial information

Trial identification

Sponsor protocol code	D-US-60010-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04083235
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Bioscience
Sponsor organisation address	One Main Street, Cambridge, MA, United States, 02142
Public contact	Medical Director, Ipsen Bioscience, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Bioscience, clinical.trials@ipsen.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	Interim
Date of interim/final analysis	23 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 July 2022
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of the regimen of irinotecan liposome injection + oxaliplatin + 5-fluorouracil (5-FU)/leucovorin (LV) [NALIRIFOX] versus nab-paclitaxel + gemcitabine in improving overall survival (OS) in participants who have not previously received chemotherapy for metastatic adenocarcinoma of the pancreas.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the International Council for Harmonization Good Clinical Practice and in compliance with independent ethics committees/institutional review boards and informed consent regulations. This study adhered to the United States of America Food and Drug Administration regulations and all applicable local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 2020
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	Portugal: 10
Country: Number of subjects enrolled	Spain: 143
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czechia: 38
Country: Number of subjects enrolled	France: 50
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Italy: 55
Country: Number of subjects enrolled	Korea, Republic of: 22
Country: Number of subjects enrolled	United States: 230
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Australia: 25
Country: Number of subjects enrolled	Brazil: 40
Country: Number of subjects enrolled	Israel: 5
Country: Number of subjects enrolled	Russian Federation: 25

Worldwide total number of subjects	770
EEA total number of subjects	398

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	384
From 65 to 84 years	385
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This Phase 3, open-label study was conducted in participants with metastatic adenocarcinoma of the pancreas at 187 investigational sites in 18 countries. First participant was recruited on 11 February 2020 and data cut-off (DCO) date 23 July 2022.

Pre-assignment

Screening details:

The study had screening period (up to 28 days), treatment period: 28-day cycles until radiologically determined disease progression per RECIST Version 1.1, unacceptable treatment related toxicity/withdrawal; survival follow-up (until death/study closure). Participants were randomized in 1:1 ratio using an interactive web response system (IWRS).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	NALIRIFOX

Arm description:

Participants were treated with irinotecan liposome injection 50 milligram per square meter (mg/m²) followed by oxaliplatin 60 mg/m², followed by LV 400 mg/m² and then 5-FU 2400 mg/m² intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle until disease progression, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Irinotecan liposome injection
Investigational medicinal product code	IPN60010
Other name	Onivyde®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered as IV infusion over 90 minutes (±10 minutes).

Investigational medicinal product name	Oxaliplatin
Investigational medicinal product code	
Other name	Eloxatin®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Oxaliplatin was administered as IV infusion over 120 minutes (±10 minutes).

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

Dosage and administration details:

LV was administered as IV infusion over 30 minutes (±5 minutes).

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU, Adrucil®

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5-FU was administered as IV infusion over 46-hours (± 120 minutes).

Arm title	Nab-paclitaxel+Gemcitabine
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Arm description:

Participants were treated with nab-paclitaxel 125 mg/m² followed by gemcitabine 1000 mg/m² IV on Days 1, 8 and 15 of each 28-day cycle until disease progression, death, unacceptable study treatment-related toxicity or withdrawal of consent.

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

Dosage and administration details:

Nab-paclitaxel was administered as IV infusion over 35 minutes (± 5 minutes).

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

Dosage and administration details:

Gemcitabine was administered as IV infusion over 30 minutes (± 5 minutes).

Number of subjects in period 1	NALIRIFOX	Nab-paclitaxel+Gemcitabine
Started	383	387
Received Treatment	370	379
Completed	59	77
Not completed	324	310
Consent withdrawn by subject	13	17
Death	252	277
Ongoing at the time of DCO	44	7
Lost to follow-up	1	1
Did not receive treatment	13	8
Does not meet entry criteria	1	-

Baseline characteristics

Reporting groups

Reporting group title	NALIRIFOX
Reporting group description:	
Participants were treated with irinotecan liposome injection 50 milligram per square meter (mg/m ²) followed by oxaliplatin 60 mg/m ² , followed by LV 400 mg/m ² and then 5-FU 2400 mg/m ² intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle until disease progression, death, unacceptable study treatment-related toxicity or withdrawal of consent.	
Reporting group title	Nab-paclitaxel+Gemcitabine
Reporting group description:	
Participants were treated with nab-paclitaxel 125 mg/m ² followed by gemcitabine 1000 mg/m ² IV on Days 1, 8 and 15 of each 28-day cycle until disease progression, death, unacceptable study treatment-related toxicity or withdrawal of consent.	

Reporting group values	NALIRIFOX	Nab-paclitaxel+Gemcitabine	Total
Number of subjects	383	387	770
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.8	64.0	
standard deviation	± 9.71	± 8.34	-
Gender categorical Units: Subjects			
Female	179	157	336
Male	204	230	434
Ethnicity Units: Subjects			
Hispanic or Latino	49	30	79
Not Hispanic or Latino	305	328	633
Not Reported	29	29	58
Race Units: Subjects			
White	315	324	639
Not Reported	26	29	55
Asian	20	18	38
Black or African American	12	7	19
Other	7	6	13
Multiple	3	0	3
American Indian or Alaska Native	0	2	2
Native Hawaiian or Other Pacific Islander	0	1	1

End points

End points reporting groups

Reporting group title	NALIRIFOX
Reporting group description: Participants were treated with irinotecan liposome injection 50 milligram per square meter (mg/m ²) followed by oxaliplatin 60 mg/m ² , followed by LV 400 mg/m ² and then 5-FU 2400 mg/m ² intravenous (IV) infusion on Days 1 and 15 of each 28-day cycle until disease progression, death, unacceptable study treatment-related toxicity or withdrawal of consent.	
Reporting group title	Nab-paclitaxel+Gemcitabine
Reporting group description: Participants were treated with nab-paclitaxel 125 mg/m ² followed by gemcitabine 1000 mg/m ² IV on Days 1, 8 and 15 of each 28-day cycle until disease progression, death, unacceptable study treatment-related toxicity or withdrawal of consent.	

Primary: OS

End point title	OS
End point description: The OS was defined as time from the date of randomization to the date of death due to any cause. Participants who did not have a date of death recorded at the time of the final analysis were censored at the last known time that the participant was alive. The median OS was measured using Kaplan-Meier technique. The Intent-to-Treat (ITT) population consisted of all randomized participants to whom study treatment was assigned by randomization.	
End point type	Primary
End point timeframe: Assessments performed at baseline (within 28 days before start of study treatment), every 8 weeks after first dose, end of treatment (EoT) visit, then every 2 months thereafter up to DCO date of 23 July 2022 (maximum of 893 days)	

End point values	NALIRIFOX	Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	387		
Units: months				
median (confidence interval 95%)	11.1 (10.0 to 12.1)	9.2 (8.3 to 10.6)		

Statistical analyses

Statistical analysis title	Treatment difference in OS
Comparison groups	NALIRIFOX v Nab-paclitaxel+Gemcitabine

Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.04
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.99

Notes:

[1] - The HR and 95% confidence interval (CI) was based on a stratified Cox proportional hazards regression model, stratified by baseline Eastern Cooperative Oncology Group (ECOG) performance status, region and liver metastases as per IWRS.

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)
End point description:	
PFS was defined as the time from the date of randomization to the first documented disease progression using response evaluation criteria in solid tumors (RECIST Version 1.1) as per Investigator assessment or death due to any cause. The median PFS was measured using Kaplan-Meier technique. The ITT population consisted of all randomized participants to whom study treatment was assigned by randomization. Only participants with PFS event are reported.	
End point type	Secondary
End point timeframe:	
Assessments performed at baseline (within 28 days before start of study treatment), every 8 weeks after first dose until EoT visit (maximum of 893 days)	

End point values	NALIRIFOX	Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	249	259		
Units: months				
median (confidence interval 95%)	7.4 (6.0 to 7.7)	5.6 (5.3 to 5.8)		

Statistical analyses

Statistical analysis title	Treatment difference in PFS
Comparison groups	NALIRIFOX v Nab-paclitaxel+Gemcitabine
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	other ^[2]
P-value	< 0.0001
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.83

Notes:

[2] - The HR and 95% CI was based on a stratified Cox proportional hazards regression model, stratified by baseline ECOG performance status, region and liver metastases as per IWRS.

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)
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End point description:

The ORR was defined as the percentage of participants with a best overall response (BOR) characterized as either a complete response or partial response per RECIST Version 1.1. BOR was defined as the best response as recorded from randomization until documented objective disease progression using RECIST Version 1.1. The ORR was calculated using Clopper-Pearson method. The ITT population consisted of all randomized participants to whom study treatment was assigned by randomization.

End point type	Secondary
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End point timeframe:

Assessments performed at baseline (within 28 days before start of study treatment), every 8 weeks after first dose until EoT visit (maximum of 893 days)

End point values	NALIRIFOX	Nab-paclitaxel+Gemcitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	383	387		
Units: percentage of participants				
number (confidence interval 95%)	41.8 (36.8 to 46.9)	36.2 (31.4 to 41.2)		

Statistical analyses

Statistical analysis title	Comparison of odds ratio (OR)
Comparison groups	NALIRIFOX v Nab-paclitaxel+Gemcitabine
Number of subjects included in analysis	770
Analysis specification	Pre-specified
Analysis type	other ^[3]
P-value	= 0.1131
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.69

Notes:

[3] - OR, 95% CI and p-value were obtained from the Cochran-Mantel-Haenszel test adjusting by baseline ECOG performance status, region and liver metastases as per IWRS.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events are reported from the time of first study treatment administration (Day 1) up to DCO date of 23 July 2022 (maximum of 893 days)

Adverse event reporting additional description:

The Safety population was a subset of the ITT population that received at least 1 dose (including a partial dose) of any component of the study medication in the combination.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	NALIRIFOX
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Reporting group description:

Participants were treated with irinotecan liposome injection 50 mg/m² followed by oxaliplatin 60 mg/m², followed by LV 400 mg/m² and then 5-FU 2400 mg/m² IV infusion on Days 1 and 15 of each 28-day cycle until disease progression, death, unacceptable study treatment-related toxicity or withdrawal of consent.

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

Participants were treated with nab-paclitaxel 125 mg/m² followed by gemcitabine 1000 mg/m² IV on Days 1, 8 and 15 of each 28-day cycle until disease progression, death, unacceptable study treatment-related toxicity or withdrawal of consent.

Serious adverse events	NALIRIFOX	Nab-paclitaxel+Gemcitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	201 / 370 (54.32%)	195 / 379 (51.45%)	
number of deaths (all causes)	252	277	
number of deaths resulting from adverse events	22	23	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Peritumoural oedema			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour pain			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	4 / 370 (1.08%)	8 / 379 (2.11%)	
occurrences causally related to treatment / all	1 / 4	2 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 370 (0.27%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Embolism arterial			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 370 (0.00%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Hypertension			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 370 (0.54%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac vein occlusion			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (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	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 370 (1.89%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	3 / 7	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site inflammation			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			

subjects affected / exposed	7 / 370 (1.89%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	4 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 370 (0.27%)	6 / 379 (1.58%)	
occurrences causally related to treatment / all	1 / 1	3 / 6	
deaths causally related to treatment / all	1 / 1	1 / 1	
Generalised oedema			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inadequate analgesia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammation			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	3 / 370 (0.81%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			

subjects affected / exposed	0 / 370 (0.00%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Performance status decreased			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 370 (2.16%)	12 / 379 (3.17%)	
occurrences causally related to treatment / all	1 / 9	4 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Penile vein thrombosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Priapism			

subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 370 (0.54%)	5 / 379 (1.32%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (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	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infiltration			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	2 / 370 (0.54%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pneumonitis aspiration			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	10 / 370 (2.70%)	7 / 379 (1.85%)	
occurrences causally related to treatment / all	3 / 10	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 370 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	2 / 370 (0.54%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Thrombosis in device			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (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	5 / 370 (1.35%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood glucose abnormal			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 370 (0.54%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (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	2 / 370 (0.54%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 370 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Exposure to SARS-CoV-2			
subjects affected / exposed	0 / 370 (0.00%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 370 (0.00%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac flutter			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	2 / 370 (0.54%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	2 / 370 (0.54%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	4 / 370 (1.08%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 4	1 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Embolic stroke			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
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 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	4 / 370 (1.08%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	1 / 2	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pineal gland cyst			

subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 370 (1.35%)	8 / 379 (2.11%)	
occurrences causally related to treatment / all	4 / 6	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile neutropenia			
subjects affected / exposed	7 / 370 (1.89%)	6 / 379 (1.58%)	
occurrences causally related to treatment / all	7 / 9	6 / 6	
deaths causally related to treatment / all	1 / 1	1 / 1	
Neutropenia			

subjects affected / exposed	2 / 370 (0.54%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 370 (0.54%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal vein occlusion			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	9 / 370 (2.43%)	8 / 379 (2.11%)	
occurrences causally related to treatment / all	2 / 10	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (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	6 / 370 (1.62%)	5 / 379 (1.32%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colitis			
subjects affected / exposed	7 / 370 (1.89%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	6 / 7	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 370 (0.27%)	6 / 379 (1.58%)	
occurrences causally related to treatment / all	0 / 1	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	23 / 370 (6.22%)	9 / 379 (2.37%)	
occurrences causally related to treatment / all	22 / 28	6 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	2 / 370 (0.54%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	2 / 370 (0.54%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	3 / 370 (0.81%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			

subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric fistula			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 370 (0.81%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal toxicity			
subjects affected / exposed	2 / 370 (0.54%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	2 / 370 (0.54%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	3 / 370 (0.81%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	3 / 370 (0.81%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal pseudo-obstruction			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric vein thrombosis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (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	18 / 370 (4.86%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	15 / 24	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	2 / 370 (0.54%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (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 / 370 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Terminal ileitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 370 (0.27%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	22 / 370 (5.95%)	6 / 379 (1.58%)	
occurrences causally related to treatment / all	15 / 26	4 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary obstruction			
subjects affected / exposed	6 / 370 (1.62%)	1 / 379 (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	4 / 370 (1.08%)	6 / 379 (1.58%)	
occurrences causally related to treatment / all	1 / 4	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholecystitis			

subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholestasis			
subjects affected / exposed	1 / 370 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis toxic			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	2 / 370 (0.54%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pruritus			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 370 (0.81%)	9 / 379 (2.37%)	
occurrences causally related to treatment / all	2 / 3	5 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 370 (0.00%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal impairment			

subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest wall haematoma			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Abdominal abscess			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asymptomatic COVID-19			
subjects affected / exposed	0 / 370 (0.00%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			

subjects affected / exposed	2 / 370 (0.54%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	18 / 370 (4.86%)	14 / 379 (3.69%)	
occurrences causally related to treatment / all	0 / 18	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Campylobacter colitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 370 (0.00%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 370 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder abscess			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	3 / 370 (0.81%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (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	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site cellulitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective spondylitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (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	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			

subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	7 / 370 (1.89%)	13 / 379 (3.43%)	
occurrences causally related to treatment / all	0 / 7	3 / 13	
deaths causally related to treatment / all	0 / 2	0 / 3	
Pneumonia aspiration			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural cellulitis			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	6 / 370 (1.62%)	16 / 379 (4.22%)	
occurrences causally related to treatment / all	4 / 6	9 / 18	
deaths causally related to treatment / all	1 / 2	5 / 8	
Septic shock			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspected COVID-19			

subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 370 (0.81%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	2 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Adult failure to thrive			
subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	5 / 370 (1.35%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	2 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	10 / 370 (2.70%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	8 / 11	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
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	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	0 / 370 (0.00%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 370 (0.00%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 370 (0.27%)	4 / 379 (1.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	6 / 370 (1.62%)	3 / 379 (0.79%)	
occurrences causally related to treatment / all	4 / 7	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 370 (0.27%)	2 / 379 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	1 / 370 (0.27%)	1 / 379 (0.26%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 370 (0.27%)	0 / 379 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	NALIRIFOX	Nab- paclitaxel+Gemcitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	364 / 370 (98.38%)	371 / 379 (97.89%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	45 / 370 (12.16%)	48 / 379 (12.66%)	
occurrences (all)	64	64	
Aspartate aminotransferase increased			
subjects affected / exposed	40 / 370 (10.81%)	40 / 379 (10.55%)	
occurrences (all)	58	55	
Blood alkaline phosphatase increased			
subjects affected / exposed	39 / 370 (10.54%)	31 / 379 (8.18%)	
occurrences (all)	42	33	
Blood bilirubin increased			
subjects affected / exposed	21 / 370 (5.68%)	22 / 379 (5.80%)	
occurrences (all)	23	23	
Gamma-glutamyltransferase increased			
subjects affected / exposed	44 / 370 (11.89%)	34 / 379 (8.97%)	
occurrences (all)	54	35	
Neutrophil count decreased			
subjects affected / exposed	73 / 370 (19.73%)	69 / 379 (18.21%)	
occurrences (all)	208	112	
Platelet count decreased			
subjects affected / exposed	39 / 370 (10.54%)	67 / 379 (17.68%)	
occurrences (all)	71	109	
Weight decreased			
subjects affected / exposed	82 / 370 (22.16%)	33 / 379 (8.71%)	
occurrences (all)	92	34	
White blood cell count decreased			
subjects affected / exposed	16 / 370 (4.32%)	32 / 379 (8.44%)	
occurrences (all)	24	54	
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	21 / 370 (5.68%) 24	15 / 379 (3.96%) 19	
Hypotension subjects affected / exposed occurrences (all)	21 / 370 (5.68%) 27	25 / 379 (6.60%) 26	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	24 / 370 (6.49%) 25	40 / 379 (10.55%) 44	
Dysgeusia subjects affected / exposed occurrences (all)	63 / 370 (17.03%) 74	58 / 379 (15.30%) 67	
Headache subjects affected / exposed occurrences (all)	23 / 370 (6.22%) 37	19 / 379 (5.01%) 24	
Neuropathy peripheral subjects affected / exposed occurrences (all)	66 / 370 (17.84%) 89	66 / 379 (17.41%) 92	
Neurotoxicity subjects affected / exposed occurrences (all)	21 / 370 (5.68%) 35	13 / 379 (3.43%) 22	
Paraesthesia subjects affected / exposed occurrences (all)	44 / 370 (11.89%) 53	33 / 379 (8.71%) 41	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	56 / 370 (15.14%) 79	51 / 379 (13.46%) 60	
Polyneuropathy subjects affected / exposed occurrences (all)	16 / 370 (4.32%) 19	19 / 379 (5.01%) 20	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	94 / 370 (25.41%) 134	151 / 379 (39.84%) 196	
Leukopenia			

subjects affected / exposed occurrences (all)	18 / 370 (4.86%) 24	40 / 379 (10.55%) 43	
Neutropenia subjects affected / exposed occurrences (all)	108 / 370 (29.19%) 264	121 / 379 (31.93%) 278	
Thrombocytopenia subjects affected / exposed occurrences (all)	50 / 370 (13.51%) 84	93 / 379 (24.54%) 173	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	110 / 370 (29.73%) 164	101 / 379 (26.65%) 166	
Chills subjects affected / exposed occurrences (all)	6 / 370 (1.62%) 6	19 / 379 (5.01%) 20	
Fatigue subjects affected / exposed occurrences (all)	120 / 370 (32.43%) 173	143 / 379 (37.73%) 183	
Mucosal inflammation subjects affected / exposed occurrences (all)	50 / 370 (13.51%) 60	16 / 379 (4.22%) 20	
Oedema peripheral subjects affected / exposed occurrences (all)	52 / 370 (14.05%) 60	107 / 379 (28.23%) 134	
Pyrexia subjects affected / exposed occurrences (all)	33 / 370 (8.92%) 43	84 / 379 (22.16%) 129	
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	22 / 370 (5.95%) 26	13 / 379 (3.43%) 15	
Abdominal pain subjects affected / exposed occurrences (all)	92 / 370 (24.86%) 110	75 / 379 (19.79%) 80	
Abdominal pain upper			

subjects affected / exposed	27 / 370 (7.30%)	21 / 379 (5.54%)	
occurrences (all)	34	29	
Constipation			
subjects affected / exposed	93 / 370 (25.14%)	113 / 379 (29.82%)	
occurrences (all)	115	141	
Diarrhoea			
subjects affected / exposed	258 / 370 (69.73%)	135 / 379 (35.62%)	
occurrences (all)	566	221	
Dry mouth			
subjects affected / exposed	28 / 370 (7.57%)	14 / 379 (3.69%)	
occurrences (all)	29	16	
Dyspepsia			
subjects affected / exposed	23 / 370 (6.22%)	18 / 379 (4.75%)	
occurrences (all)	32	20	
Flatulence			
subjects affected / exposed	30 / 370 (8.11%)	18 / 379 (4.75%)	
occurrences (all)	33	21	
Haemorrhoids			
subjects affected / exposed	19 / 370 (5.14%)	12 / 379 (3.17%)	
occurrences (all)	22	13	
Nausea			
subjects affected / exposed	215 / 370 (58.11%)	162 / 379 (42.74%)	
occurrences (all)	406	216	
Stomatitis			
subjects affected / exposed	50 / 370 (13.51%)	45 / 379 (11.87%)	
occurrences (all)	81	54	
Vomiting			
subjects affected / exposed	139 / 370 (37.57%)	96 / 379 (25.33%)	
occurrences (all)	222	168	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 370 (3.78%)	30 / 379 (7.92%)	
occurrences (all)	18	31	
Dyspnoea			

subjects affected / exposed occurrences (all)	24 / 370 (6.49%) 28	45 / 379 (11.87%) 48	
Epistaxis subjects affected / exposed occurrences (all)	14 / 370 (3.78%) 15	43 / 379 (11.35%) 49	
Pulmonary embolism subjects affected / exposed occurrences (all)	20 / 370 (5.41%) 20	24 / 379 (6.33%) 24	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	52 / 370 (14.05%) 53	119 / 379 (31.40%) 120	
Pruritus subjects affected / exposed occurrences (all)	12 / 370 (3.24%) 14	22 / 379 (5.80%) 26	
Rash subjects affected / exposed occurrences (all)	11 / 370 (2.97%) 12	34 / 379 (8.97%) 37	
Rash maculo-papular subjects affected / exposed occurrences (all)	3 / 370 (0.81%) 3	25 / 379 (6.60%) 30	
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	10 / 370 (2.70%) 10	24 / 379 (6.33%) 25	
Insomnia subjects affected / exposed occurrences (all)	28 / 370 (7.57%) 28	32 / 379 (8.44%) 32	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	13 / 370 (3.51%) 16	30 / 379 (7.92%) 41	
Back pain subjects affected / exposed occurrences (all)	28 / 370 (7.57%) 37	33 / 379 (8.71%) 36	
Muscular weakness			

subjects affected / exposed occurrences (all)	17 / 370 (4.59%) 22	21 / 379 (5.54%) 24	
Myalgia subjects affected / exposed occurrences (all)	13 / 370 (3.51%) 15	31 / 379 (8.18%) 43	
Pain in extremity subjects affected / exposed occurrences (all)	7 / 370 (1.89%) 8	30 / 379 (7.92%) 35	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	27 / 370 (7.30%) 29	23 / 379 (6.07%) 29	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	132 / 370 (35.68%) 157	68 / 379 (17.94%) 136	
Dehydration subjects affected / exposed occurrences (all)	35 / 370 (9.46%) 40	29 / 379 (7.65%) 31	
Hypoalbuminaemia subjects affected / exposed occurrences (all)	26 / 370 (7.03%) 33	30 / 379 (7.92%) 31	
Hypokalaemia subjects affected / exposed occurrences (all)	116 / 370 (31.35%) 190	49 / 379 (12.93%) 70	
Hypomagnesaemia subjects affected / exposed occurrences (all)	34 / 370 (9.19%) 44	16 / 379 (4.22%) 22	
Hyponatraemia subjects affected / exposed occurrences (all)	18 / 370 (4.86%) 21	20 / 379 (5.28%) 21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 November 2019	The study name was updated with the branding logo. Study duration was clarified. Adverse event causality assessment clarified by the investigator. Adverse events of special interest were defined as thromboembolic disease. Collection of electronic serious adverse events (SAE) were clarified. Clarification that disease progression was not classified as an SAE. The use of contraceptive were aligned with all packaging information in all localities of the study. Minor editorial changes to provide additional details.
03 June 2020	The electrocardiogram assessment timepoint were clarified.
19 August 2021	Eligibility criterion and protocol procedures were clarified. Details specific to conduct of the study during the COVID-19 pandemic were added. Secondary endpoint analysis was updated to refine the interim analysis of OS.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported