Clinical trial results:
A randomized, open-label, Phase 2 study of nanoliposomal irinotecan (nal-IRI)-containing regimens versus nab-paclitaxel plus gemcitabine in patients with previously untreated, metastatic pancreatic adenocarcinoma

Summary

EudraCT number	2015-003086-28
Trial protocol	SE ES GB BE FR IT
Global end of trial date	15 February 2021

Results information

Result version number	v1 (current)
This version publication date	06 June 2022
First version publication date	06 June 2022

Trial information

Trial identification

Sponsor protocol code	MM-398-07-02-03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02551991
WHO universal trial number (UTN)	-
Other trial identifiers	IND No. : 102799

Notes:

Sponsors

Sponsor organisation name	Ipsen Bioscience, Inc.
Sponsor organisation address	650 East Kendall Street, Cambridge, Massachusetts, United States, 02142
Public contact	Medical Director, Ipsen Bioscience, Inc., clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Bioscience, Inc., 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	Final
Date of interim/final analysis	15 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• To evaluate the safety and tolerability of irinotecan liposome injection + 5-fluorouracil (5-FU)/leucovorin (LV) + oxaliplatin.
• To characterize dose limiting toxicities (DLTs) associated with irinotecan liposome injection +5-FU/LV + oxaliplatin and determine the recommended dose of the triplet combination for future development.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice and in compliance with Independent Ethics Committees/Institutional Review Boards and informed consent regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	56
EEA total number of subjects	6

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)	34

From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 2 non-comparative, open-label study was conducted in previously untreated metastatic pancreatic cancer participants at 15 investigational sites.

Pre-assignment

Screening details:

This study was divided into 2 parts: Part 1 (dose exploration [Part 1A] followed by dose expansion [Part 1B] of irinotecan liposome injection + 5-FU/LV + oxaliplatin regimen) and Part 2 (comparison of irinotecan liposome injection-containing regimen versus [vs] nab-paclitaxel plus gemcitabine). Overall, 56 participants were enrolled in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Dose Exploration: Cohort 1

Arm description:

Participants received irinotecan liposome injection 70 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.

Arm type	Experimental
Investigational medicinal product name	Irinotecan liposome injection
Investigational medicinal product code	MM-398
Other name	Nal-IRI, BAX2398, PEP02, Onivyde
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered as an IV infusion over 90 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

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

Dosage and administration details:

Oxaliplatin was administered as an IV infusion over 120 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	LV
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

LV was administered as an IV infusion over 30 minutes (±5 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5-FU was administered as an IV infusion over 46-hours (±60 minutes) on Days 1 and 15 of each 28-day cycle.

Arm title	Dose Exploration: Cohort -1

Arm description:

Participants received irinotecan liposome injection 50 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 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	MM-398
Other name	Nal-IRI, BAX2398, PEP02, Onivyde
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered as an IV infusion over 90 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

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

Dosage and administration details:

Oxaliplatin was administered as an IV infusion over 120 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	LV
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

LV was administered as an IV infusion over 30 minutes (±5 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5-FU was administered as an IV infusion over 46-hours (±60 minutes) on Days 1 and 15 of each 28-day cycle.

Arm title	Dose Exploration: Cohort -2B

Arm description:

Participants received irinotecan liposome injection 50 mg/m^2 followed by oxaliplatin 85 mg/m^2 followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 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	MM-398
Other name	Nal-IRI, BAX2398, PEP02, Onivyde
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered as an IV infusion over 90 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

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

Dosage and administration details:

Oxaliplatin was administered as an IV infusion over 120 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	LV
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

LV was administered as an IV infusion over 30 minutes (±5 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5-FU was administered as an IV infusion over 46-hours (±60 minutes) on Days 1 and 15 of each 28-day cycle.

Arm title	Dose Exploration: Cohort -3

Arm description:

Participants received irinotecan liposome injection 55 mg/m^2 followed by oxaliplatin 70 mg/m^2 followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 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	MM-398
Other name	Nal-IRI, BAX2398, PEP02, Onivyde
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered as an IV infusion over 90 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

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

Dosage and administration details:

Oxaliplatin was administered as an IV infusion over 120 minutes (±10 minutes) on Days 1 and 15 of

each 28-day cycle.

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	LV
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

LV was administered as an IV infusion over 30 minutes (±5 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5-FU was administered as an IV infusion over 46-hours (±60 minutes) on Days 1 and 15 of each 28-day cycle.

Arm title	Dose Expansion: Cohort -1

Arm description:

Participants received irinotecan liposome injection 50 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 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	MM-398
Other name	Nal-IRI, BAX2398, PEP02, Onivyde
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Irinotecan liposome injection was administered as an IV infusion over 90 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

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

Dosage and administration details:

Oxaliplatin was administered as an IV infusion over 120 minutes (±10 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	LV
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

LV was administered as an IV infusion over 30 minutes (±5 minutes) on Days 1 and 15 of each 28-day cycle.

Investigational medicinal product name	5-Fluorouracil
Investigational medicinal product code	
Other name	5-FU
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

5-FU was administered as an IV infusion over 46-hours (±60 minutes) on Days 1 and 15 of each 28-day cycle.

Number of subjects in period 1	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B
Started	7	7	10
Completed	0	0	0
Not completed	7	7	10
Consent withdrawn by subject	1	-	-
Death	5	7	8
Sponsor Decision	1	-	1
Unspecified	-	-	-
Lost to follow-up	-	-	1

Number of subjects in period 1	Dose Exploration: Cohort -3	Dose Expansion: Cohort -1
Started	7	25
Completed	0	0
Not completed	7	25
Consent withdrawn by subject	-	2
Death	7	17
Sponsor Decision	-	5
Unspecified	-	1
Lost to follow-up	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Dose Exploration: Cohort 1
Reporting group description:	
Participants received irinotecan liposome injection 70 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	Dose Exploration: Cohort -1
Reporting group description:	
Participants received irinotecan liposome injection 50 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 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	Dose Exploration: Cohort -2B
Reporting group description:	
Participants received irinotecan liposome injection 50 mg/m^2 followed by oxaliplatin 85 mg/m^2 followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 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	Dose Exploration: Cohort -3
Reporting group description:	
Participants received irinotecan liposome injection 55 mg/m^2 followed by oxaliplatin 70 mg/m^2 followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 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	Dose Expansion: Cohort -1
Reporting group description:	
Participants received irinotecan liposome injection 50 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 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 values	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B
Number of subjects	7	7	10
Age categorical Units: Subjects			
< 65 years	4	4	3
>= 65 years	3	3	7
Gender categorical Units: Subjects			
Female	6	4	2
Male	1	3	8
Race Units: Subjects			
White	6	7	9
Black or African American	0	0	0
Asian	1	0	1
Not Reportable	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0

Not Hispanic or Latino	7	7	10

Reporting group values	Dose Exploration: Cohort -3	Dose Expansion: Cohort -1	Total
Number of subjects	7	25	56
Age categorical Units: Subjects			
< 65 years	4	19	34
>= 65 years	3	6	22
Gender categorical Units: Subjects			
Female	2	14	28
Male	5	11	28
Race Units: Subjects			
White	7	21	50
Black or African American	0	2	2
Asian	0	1	3
Not Reportable	0	1	1
Ethnicity Units: Subjects			
Hispanic or Latino	0	4	4
Not Hispanic or Latino	7	21	52

End points

End points reporting groups

Reporting group title	Dose Exploration: Cohort 1

Reporting group description:

Participants received irinotecan liposome injection 70 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	Dose Exploration: Cohort -1

Reporting group description:

Participants received irinotecan liposome injection 50 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 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	Dose Exploration: Cohort -2B

Reporting group description:

Participants received irinotecan liposome injection 50 mg/m^2 followed by oxaliplatin 85 mg/m^2 followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 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	Dose Exploration: Cohort -3

Reporting group description:

Participants received irinotecan liposome injection 55 mg/m^2 followed by oxaliplatin 70 mg/m^2 followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 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	Dose Expansion: Cohort -1

Reporting group description:

Participants received irinotecan liposome injection 50 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 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.

Subject analysis set title	Cohort -1: Pooled
Subject analysis set type	Full analysis

Subject analysis set description:

Participants received irinotecan liposome injection 50 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 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.

Primary: Part 1A: Number of Participants With Dose-Limiting Toxicities (DLT)

End point title	Part 1A: Number of Participants With Dose-Limiting Toxicities (DLT)[1][2]

End point description:

Adverse events (AEs) were considered to be DLTs if they occurred during the safety evaluation period (i.e, 28 days of Cycle 1; or 14 days after the second dose of study treatment if there was a treatment delay) and were deemed related to the study treatment regimen. Any AE that was related to disease progression was not considered a DLT. Safety population included participants who received at least 1 dose of any study treatment.

End point type	Primary

End point timeframe:

From the start of the first study treatment (Cycle 1 Day 1) up to 14 days after the second dose of study treatment, maximum of 42 days

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: Only descriptive statistical analysis was performed for the primary endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants treated in Part 1A (dose exploration) were analyzed for the primary endpoint.

End point values	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B	Dose Exploration: Cohort -3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	10	7
Units: participants	2	1	2	0

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression Free Survival (PFS)

End point title	Median Progression Free Survival (PFS)

End point description:

The PFS was defined as the time from date of first study treatment to the first documented radiographical progression of disease (PD), per investigator using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1, or death from any cause, whichever comes first. The PFS was calculated using Kaplan-Meier technique. Safety population included participants who received at least 1 dose of any study treatment. 99999= Upper limit of confidence interval was not evaluable.

End point type	Secondary

End point timeframe:

RECIST 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 (maximum of 278 weeks).

End point values	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B	Dose Exploration: Cohort -3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	10	7
Units: months				
number (confidence interval 95%)	9.7 (2.96 to 99999)	32.3 (0.53 to 99999)	9.2 (0.46 to 99999)	3.8 (1.22 to 5.78)

End point values	Dose Expansion: Cohort -1	Cohort -1: Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	32		

Units: months				
number (confidence interval 95%)	9.2 (7.59 to 11.20)	9.2 (7.59 to 11.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response (BOR)

End point title	Best Overall Response (BOR)

End point description:

The BOR was defined as the best response (complete response [CR] + partial response [PR] + stable disease [SD]) recorded from the start of study treatment until disease progression or start of new anticancer therapy. Safety population included participants who received at least 1 dose of any study treatment.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), every 8 weeks after first dose, EoT visit, then every 2 months thereafter (maximum of 278 weeks).

End point values	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B	Dose Exploration: Cohort -3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	10	7
Units: participants	2	6	4	4

End point values	Dose Expansion: Cohort -1	Cohort -1: Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	32		
Units: participants	20	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

The ORR was defined as the percentage of participants with a BOR characterized as either a CR or PR relative to the total number of evaluable participants. Evaluable participants were defined as treated participants with measurable disease at baseline. Safety population included participants who received

at least 1 dose of any study treatment.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), every 8 weeks after first dose, EoT visit, then every 2 months thereafter (maximum of 278 weeks).

End point values	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B	Dose Exploration: Cohort -3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	10	7
Units: percentage of participants				
number (confidence interval 95%)	0 (0 to 41.0)	42.9 (9.9 to 81.6)	30.0 (6.7 to 65.2)	14.3 (0.4 to 57.9)

End point values	Dose Expansion: Cohort -1	Cohort -1: Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	32		
Units: percentage of participants				
number (confidence interval 95%)	32.0 (14.9 to 53.5)	34.4 (18.6 to 53.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

The DCR was defined as percentage of participants with CR or PR or SD, per RECIST Version 1.1 relative to total number of treated participants with measurable disease at baseline. Safety population included participants who received at least 1 dose of any study treatment.

End point type	Secondary

End point timeframe:

At Week 16

End point values	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B	Dose Exploration: Cohort -3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	10	7
Units: percentage of participants				
number (confidence interval 95%)	42.9 (9.9 to 81.6)	71.4 (29.0 to 96.3)	40.0 (12.2 to 73.8)	28.6 (3.7 to 71.0)

End point values	Dose Expansion: Cohort -1	Cohort -1: Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	32		
Units: percentage of participants				
number (confidence interval 95%)	72.0 (50.6 to 87.9)	71.9 (53.3 to 86.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Overall Survival (OS)

End point title	Median Overall Survival (OS)

End point description:

The OS was the time from date of first study treatment to the date of death from any cause. Participant survival data were collected from all available sources. The OS was calculated using Kaplan-Meier technique. Safety population included participants who received at least 1 dose of any study treatment.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), every 8 weeks after first dose, EoT visit, then every 2 months thereafter (maximum of 278 weeks).

End point values	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B	Dose Exploration: Cohort -3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	10	7
Units: months				
median (confidence interval 95%)	12.6 (3.98 to 21.03)	12.5 (0.53 to 12.71)	16.6 (0.69 to 26.74)	5.8 (1.35 to 14.65)

End point values	Dose Expansion: Cohort -1	Cohort -1: Pooled		

Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	25	32		
Units: months				
median (confidence interval 95%)	12.7 (8.18 to 23.66)	12.6 (8.74 to 19.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Median Duration of Response (DoR)

End point title	Median Duration of Response (DoR)

End point description:

The DoR was defined as the time from the first date of response (CR or PR) to first date of documented radiographical PD, per investigator using RECIST Version 1.1. This only applied to participants with CR or PR. If a participant was given a new anticancer therapy prior to first response, DoR was not calculated. The DoR was calculated using Kaplan-Meier technique. Safety population included participants who received at least 1 dose of any study treatment. Only participants with DoR events were analyzed for this outcome measure. -9999= Median was not evaluable, -99999= Lower limit of confidence interval was not evaluable, and 99999= Upper limit of confidence interval was not evaluable.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), every 8 weeks after first dose, EoT visit, then every 2 months thereafter (maximum of 278 weeks).

End point values	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B	Dose Exploration: Cohort -3
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[3]	2	1	0[4]
Units: months				
median (confidence interval 95%)	(to)	28.4 (3.52 to 99999)	-9999 (-99999 to 16.39)	(to)

Notes:

[3] - No participants with DoR events.

[4] - No participants with DoR events.

End point values	Dose Expansion: Cohort -1	Cohort -1: Pooled		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	4	6		
Units: months				
median (confidence interval 95%)	9.4 (2.20 to 99999)	9.4 (3.52 to 99999)		

Statistical analyses

No statistical analyses for this end point

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 30 days after the date of last study treatment administration or until the start of alternative anticancer therapy, approximately 1008 days.

Adverse event reporting additional description:

Safety population included participants who received at least 1 dose of any study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Dose Exploration: Cohort 1

Reporting group description:

Participants received irinotecan liposome injection 70 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 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	Dose Exploration: Cohort -1

Reporting group description:

Participants received irinotecan liposome injection 50 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 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	Dose Exploration: Cohort -2B

Reporting group description:

Participants received irinotecan liposome injection 50 mg/m^2 followed by oxaliplatin 85 mg/m^2 followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 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	Dose Exploration: Cohort -3

Reporting group description:

Participants received irinotecan liposome injection 55 mg/m^2 followed by oxaliplatin 70 mg/m^2 followed by LV 400 mg/m^2 and then 5-FU 2400 mg/m^2 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	Dose Expansion: Cohort -1

Reporting group description:

Participants received irinotecan liposome injection 50 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 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.

Serious adverse events	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	2 / 7 (28.57%)	7 / 10 (70.00%)
number of deaths (all causes)	5	7	8
number of deaths resulting from adverse events	0	1	1

Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia of malignant disease			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant gastrointestinal obstruction			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary dilatation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dose Exploration: Cohort -3	Dose Expansion: Cohort -1	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	15 / 25 (60.00%)	
number of deaths (all causes)	7	17	
number of deaths resulting from adverse events	1	2	

Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arteriospasm coronary			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia of malignant disease			

subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (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			
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (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	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 7 (42.86%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	2 / 7 (28.57%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant gastrointestinal obstruction			

subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
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			

Pulmonary embolism			
subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
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	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacterial sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
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	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dose Exploration: Cohort 1	Dose Exploration: Cohort -1	Dose Exploration: Cohort -2B
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	7 / 7 (100.00%)	10 / 10 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	4 / 7 (57.14%)	0 / 10 (0.00%)
occurrences (all)	5	8	0
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	3
Orthostatic hypotension			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Vascular occlusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 7 (71.43%)	5 / 7 (71.43%)	7 / 10 (70.00%)
occurrences (all)	9	10	13
Pyrexia			
subjects affected / exposed	3 / 7 (42.86%)	1 / 7 (14.29%)	2 / 10 (20.00%)
occurrences (all)	3	1	2
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	1 / 10 (10.00%)
occurrences (all)	3	2	3
Chills			

subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Temperature intolerance			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Axillary pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Catheter site erythema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Catheter site extravasation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Catheter site haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Catheter site pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Cyst			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Vulvovaginal swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	2	0	3
Cough			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	6
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hiccups			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Sinus congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Catarrh			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Dysphonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Laryngeal oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nasal dryness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pharyngeal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 7 (14.29%)	5 / 7 (71.43%)	1 / 10 (10.00%)
occurrences (all)	1	6	1

Insomnia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Anxiety			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	1
Confusional state			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Hallucination			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Investigations			
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	4 / 10 (40.00%)
occurrences (all)	2	3	6
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	2	2	2
White blood cell count decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	2 / 10 (20.00%)
occurrences (all)	1	1	2
Neutrophil count decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	1	0	7
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Alanine aminotransferase			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Blood magnesium decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cardiac murmur			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Liver function test increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Lung diffusion test decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urine output decreased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	4	1	1
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Tooth fracture			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Animal scratch			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ligament sprain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Skin abrasion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Subdural haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Arteriospasm coronary			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Palpitations			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			

Dizziness			
subjects affected / exposed	2 / 7 (28.57%)	2 / 7 (28.57%)	3 / 10 (30.00%)
occurrences (all)	5	2	6
Neuropathy peripheral			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	2 / 10 (20.00%)
occurrences (all)	1	6	3
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	2 / 10 (20.00%)
occurrences (all)	2	2	2
Headache			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
Peripheral sensory neuropathy			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	3 / 10 (30.00%)
occurrences (all)	2	1	5
Taste disorder			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Lethargy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Neurotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cognitive disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dysaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Lhermitte's sign			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Memory impairment			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	2 / 7 (28.57%)	3 / 7 (42.86%)	5 / 10 (50.00%)
occurrences (all)	4	13	6
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	4 / 10 (40.00%)
occurrences (all)	0	10	4
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	3 / 10 (30.00%)
occurrences (all)	2	1	5
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Neutrophilia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Anaemia of malignant disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cytopenia			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Splenic infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Splenic vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Eyelid oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 7 (71.43%)	6 / 7 (85.71%)	9 / 10 (90.00%)
occurrences (all)	9	7	19
Diarrhoea			
subjects affected / exposed	6 / 7 (85.71%)	5 / 7 (71.43%)	6 / 10 (60.00%)
occurrences (all)	18	22	14
Vomiting			
subjects affected / exposed	5 / 7 (71.43%)	4 / 7 (57.14%)	5 / 10 (50.00%)
occurrences (all)	12	7	8
Constipation			
subjects affected / exposed	3 / 7 (42.86%)	4 / 7 (57.14%)	4 / 10 (40.00%)
occurrences (all)	3	9	5
Abdominal pain			
subjects affected / exposed	2 / 7 (28.57%)	3 / 7 (42.86%)	3 / 10 (30.00%)
occurrences (all)	5	5	3
Stomatitis			

subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 10 (20.00%)
occurrences (all)	0	1	7
Abdominal distension			
subjects affected / exposed	3 / 7 (42.86%)	2 / 7 (28.57%)	2 / 10 (20.00%)
occurrences (all)	3	2	2
Dry mouth			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	4	1	1
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	4 / 7 (57.14%)	2 / 10 (20.00%)
occurrences (all)	0	5	2
Abdominal pain upper			
subjects affected / exposed	2 / 7 (28.57%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
Haemorrhoids			
subjects affected / exposed	1 / 7 (14.29%)	2 / 7 (28.57%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Pancreatic failure			
subjects affected / exposed	0 / 7 (0.00%)	3 / 7 (42.86%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Colitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Anal fissure			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	2 / 10 (20.00%)
occurrences (all)	0	1	3
Small intestinal obstruction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Anal haemorrhage			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Enterocolitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	2 / 7 (28.57%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Proctalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	4
Abdominal pain lower			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Abdominal rigidity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Anal incontinence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Anal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Angular cheilitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Duodenal ulcer			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	2
Enteritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Epigastric discomfort			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Eructation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Faeces discoloured			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal oedema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Large intestinal obstruction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Large intestine perforation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Malignant gastrointestinal			

obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Odynophagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Oesophageal ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oral pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Steatorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Tongue discolouration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Varices oesophageal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Biliary dilatation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cholangitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Cholecystitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Hepatotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Portal vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 7 (42.86%)	0 / 10 (0.00%)
occurrences (all)	1	3	0
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Rash			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Decubitus ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nail discolouration			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Nail ridging			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Pain of skin			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Petechiae			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Prurigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Micturition urgency			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Oliguria			

subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Pollakiuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Ureterolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Urinary retention			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Arthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Flank pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Joint stiffness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Periarthritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Pneumonia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	1	0	2
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Bacterial sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Candida infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0

Clostridium difficile colitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Fungal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	0	1	0
Helicobacter infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Neutropenic infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Neutropenic sepsis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Septic shock			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Vulvovaginitis trichomonal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 7 (71.43%)	6 / 7 (85.71%)	4 / 10 (40.00%)
occurrences (all)	10	9	8
Hypokalaemia			
subjects affected / exposed	4 / 7 (57.14%)	2 / 7 (28.57%)	5 / 10 (50.00%)
occurrences (all)	5	3	6
Dehydration			
subjects affected / exposed	4 / 7 (57.14%)	3 / 7 (42.86%)	3 / 10 (30.00%)
occurrences (all)	5	3	4
Hypomagnesaemia			
subjects affected / exposed	3 / 7 (42.86%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	4	0	3
Hypoalbuminaemia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	4	0	3
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	2 / 10 (20.00%)
occurrences (all)	0	0	2
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypophosphataemia			

subjects affected / exposed	1 / 7 (14.29%)	1 / 7 (14.29%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	0	0	0
Hypovolaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0
Metabolic acidosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 7 (0.00%)	0 / 10 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Dose Exploration: Cohort -3	Dose Expansion: Cohort -1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	25 / 25 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Deep vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Hypotension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Orthostatic hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Vascular occlusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	5 / 7 (71.43%)	16 / 25 (64.00%)	
occurrences (all)	6	21	
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	5 / 25 (20.00%)	
occurrences (all)	1	14	
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	8 / 25 (32.00%)	
occurrences (all)	1	15	
Oedema peripheral			
subjects affected / exposed	1 / 7 (14.29%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Chills			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	2	
Mucosal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	7	
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Temperature intolerance			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Axillary pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Catheter site erythema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Catheter site extravasation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Catheter site haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	

Catheter site pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Cyst			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Disease progression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Vulvovaginal swelling			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 7 (28.57%)	2 / 25 (8.00%)	
occurrences (all)	2	2	
Cough			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Pulmonary embolism			
subjects affected / exposed	2 / 7 (28.57%)	2 / 25 (8.00%)	
occurrences (all)	3	2	
Epistaxis			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	

Hiccups			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Nasal congestion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Sinus congestion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Catarrh			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Dyspnoea exertional			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Haemoptysis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Laryngeal oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	6	
Nasal dryness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Pharyngeal inflammation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	

Pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Respiratory failure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Upper-airway cough syndrome			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 7 (14.29%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Insomnia			
subjects affected / exposed	2 / 7 (28.57%)	5 / 25 (20.00%)	
occurrences (all)	2	6	
Anxiety			
subjects affected / exposed	2 / 7 (28.57%)	3 / 25 (12.00%)	
occurrences (all)	2	3	
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Hallucination			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Irritability			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Investigations			
Weight decreased			
subjects affected / exposed	2 / 7 (28.57%)	5 / 25 (20.00%)	
occurrences (all)	4	7	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	9 / 25 (36.00%)	
occurrences (all)	1	17	
Aspartate aminotransferase increased			

subjects affected / exposed	0 / 7 (0.00%)	9 / 25 (36.00%)		
occurrences (all)	0	15		
Platelet count decreased				
subjects affected / exposed	0 / 7 (0.00%)	5 / 25 (20.00%)		
occurrences (all)	0	17		
White blood cell count decreased				
subjects affected / exposed	0 / 7 (0.00%)	4 / 25 (16.00%)		
occurrences (all)	0	10		
Neutrophil count decreased				
subjects affected / exposed	1 / 7 (14.29%)	4 / 25 (16.00%)		
occurrences (all)	1	12		
Blood alkaline phosphatase increased				
subjects affected / exposed	0 / 7 (0.00%)	4 / 25 (16.00%)		
occurrences (all)	0	17		
Blood bilirubin increased				
subjects affected / exposed	0 / 7 (0.00%)	4 / 25 (16.00%)		
occurrences (all)	0	4		
Lymphocyte count decreased				
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)		
occurrences (all)	0	23		
Gamma-glutamyltransferase increased				
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)		
occurrences (all)	0	2		
Alanine aminotransferase				
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)		
occurrences (all)	0	1		
Blood creatinine increased				
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)		
occurrences (all)	0	4		
Blood magnesium decreased				
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)		
occurrences (all)	0	1		
Cardiac murmur				
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)		
occurrences (all)	0	0		

Liver function test increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Lung diffusion test decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Urine output decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Contusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Tooth fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Animal scratch			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Skin abrasion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Subdural haematoma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Arteriospasm coronary			

subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Palpitations			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 7 (28.57%)	8 / 25 (32.00%)	
occurrences (all)	2	9	
Neuropathy peripheral			
subjects affected / exposed	2 / 7 (28.57%)	7 / 25 (28.00%)	
occurrences (all)	5	11	
Dysgeusia			
subjects affected / exposed	2 / 7 (28.57%)	4 / 25 (16.00%)	
occurrences (all)	2	5	
Headache			
subjects affected / exposed	0 / 7 (0.00%)	4 / 25 (16.00%)	
occurrences (all)	0	4	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	7	
Taste disorder			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Neurotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	3	
Cognitive disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	

Dysaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Hyperaesthesia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Lhermitte's sign			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Memory impairment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Syncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	10 / 25 (40.00%)	
occurrences (all)	2	29	
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	9 / 25 (36.00%)	
occurrences (all)	0	18	
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	7 / 25 (28.00%)	
occurrences (all)	2	35	
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	4	
Leukocytosis			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Leukopenia			

subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Neutrophilia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Anaemia of malignant disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Cytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Splenic infarction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Splenic vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye disorder			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Eyelid oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 7 (71.43%)	23 / 25 (92.00%)	
occurrences (all)	6	49	
Diarrhoea			
subjects affected / exposed	6 / 7 (85.71%)	22 / 25 (88.00%)	
occurrences (all)	14	54	
Vomiting			

subjects affected / exposed	3 / 7 (42.86%)	14 / 25 (56.00%)	
occurrences (all)	4	28	
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	13 / 25 (52.00%)	
occurrences (all)	2	22	
Abdominal pain			
subjects affected / exposed	4 / 7 (57.14%)	8 / 25 (32.00%)	
occurrences (all)	6	16	
Stomatitis			
subjects affected / exposed	1 / 7 (14.29%)	7 / 25 (28.00%)	
occurrences (all)	1	9	
Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Dry mouth			
subjects affected / exposed	3 / 7 (42.86%)	3 / 25 (12.00%)	
occurrences (all)	3	3	
Flatulence			
subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Haemorrhoids			
subjects affected / exposed	1 / 7 (14.29%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Pancreatic failure			
subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Colitis			
subjects affected / exposed	2 / 7 (28.57%)	1 / 25 (4.00%)	
occurrences (all)	3	1	
Dyspepsia			
subjects affected / exposed	0 / 7 (0.00%)	4 / 25 (16.00%)	
occurrences (all)	0	6	
Anal fissure			

subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Small intestinal obstruction			
subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences (all)	1	2	
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Anal haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Dysphagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Enterocolitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Proctalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Abdominal pain lower			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Abdominal rigidity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	4	
Anal incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Anal inflammation			

subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Angular cheilitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Duodenal ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Enteritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Epigastric discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Eructation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Faeces discoloured			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Haematemesis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Intestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Large intestinal obstruction			

subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Large intestine perforation			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Malignant gastrointestinal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Oesophageal ulcer			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	2	
Oesophagitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Pancreatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	2	
Steatorrhoea			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	

Tongue discolouration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Varices oesophageal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Biliary dilatation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Cholangitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Cholecystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Hepatotoxicity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Portal vein thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 7 (14.29%)	4 / 25 (16.00%)	
occurrences (all)	1	5	
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Rash			

subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	2	
Decubitus ulcer			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Ingrowing nail			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Nail discolouration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Nail ridging			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Pain of skin			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Petechiae			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Prurigo			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 7 (28.57%)	0 / 25 (0.00%)	
occurrences (all)	2	0	
Micturition urgency			

subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Oliguria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Pollakiuria			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Ureterolithiasis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Urinary retention			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	6	
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Muscular weakness			

subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	3 / 25 (12.00%)	
occurrences (all)	0	3	
Arthritis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 25 (4.00%)	
occurrences (all)	1	1	
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Joint stiffness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Periarthritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 7 (14.29%)	2 / 25 (8.00%)	
occurrences (all)	1	2	
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	

Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Bacterial sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Candida infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Clostridium difficile colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Fungal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Helicobacter infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Neutropenic infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Neutropenic sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	

Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	2	
Septic shock			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Tooth infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	2	
Vulvovaginitis trichomonal			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 7 (42.86%)	12 / 25 (48.00%)	
occurrences (all)	4	15	
Hypokalaemia			
subjects affected / exposed	3 / 7 (42.86%)	12 / 25 (48.00%)	
occurrences (all)	11	34	
Dehydration			
subjects affected / exposed	2 / 7 (28.57%)	5 / 25 (20.00%)	
occurrences (all)	2	7	
Hypomagnesaemia			
subjects affected / exposed	2 / 7 (28.57%)	4 / 25 (16.00%)	
occurrences (all)	2	21	
Hypoalbuminaemia			
subjects affected / exposed	1 / 7 (14.29%)	3 / 25 (12.00%)	
occurrences (all)	1	9	
Hypocalcaemia			

subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	10	
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 25 (8.00%)	
occurrences (all)	0	18	
Hyponatraemia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 25 (8.00%)	
occurrences (all)	1	18	
Hypophosphataemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 25 (0.00%)	
occurrences (all)	1	0	
Hyperphosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 25 (4.00%)	
occurrences (all)	0	1	
Hypovolaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	
Metabolic acidosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 25 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2016	To address changes to the planned statistical analyses and to incorporate the addition of ECG studies paired with time-matched PK sampling to assess possible changes in QTC intervals.
28 December 2016	To amend the original evaluation plan when dose levels 1 and -1 had been evaluated. The next dose level to be evaluated was to be level -2B, and dose levels 2 and -2A were not to be evaluated in the study. Therefore, the starting dose of irinotecan liposome injection in Part 2 would be 50 mg/m^2 and starting dose for oxaliplatin would be either 60 mg/m^2 or 85 mg/m^2 depending on findings from dose level -2B. Final determination of Part 2 dose of oxaliplatin for reporting group 1 would be made by the DLT review committee (i.e. the Part 1 Investigators, the Medical Monitor, and the Sponsor) and would be based upon careful review of DLTs, SAEs, and Grade 3-4 AEs which occurred in Part 1. To amend exclusion criteria to align with most stringent comparator drug.
03 April 2017	To change the study sponsor from Merrimack to Ipsen Bioscience.
29 September 2017	To divide Part 1 of the study into 2 phases: Part 1A (dose escalation phase enrolling small cohorts of participants progressively) and Part 1B (dose expansion intended to enroll 24 additional participants). To optimize the NAPOX regimen (irinotecan liposome injection +5-FU/LV + oxaliplatin) in participants with metastatic pancreatic adenocarcinoma by assessing an additional dose for the combination regimen (Part 1A). A new dose level cohort -3 (oxaliplatin 70 mg/m^2 + irinotecan liposome injection 55 mg/m^2) was introduced for evaluation in Part 1A following the completion of 3 dose level cohorts (1, -1 and -2B). To add another secondary objective for the Part 1 evaluation: To evaluate efficacy signals with irinotecan liposome injection in combination with 5-FU/LV + oxaliplatin using ORR (CR + PR, per RECIST v1.1), DCR (CR + PR + SD, per RECIST v1.1), DOR, PFS and OS. To expand the study sample size (Part 1B), once the dose was selected from Part 1A, to further evaluate the safety and efficacy signals and update the study design accordingly: to increase the number of participants enrolled in Part 1 from 6-18 to 54 participants. Therefore, the total enrolment for the study was increased from approximately 156-168 to 204 participants. To provide further details and add that the starting dose for all participants in Part 1 would be as per the dosing table regardless of UGT1A1*28, whereas previously participants receiving 70 mg/m^2 of irinotecan liposome injection could have the dose reduced depending on the overall safety profile seen after the first dose. In addition to the ECOG performance status, KPS was also to be recorded at Screening and within 72 hours of enrolment/randomization. An additional Appendix 3 was added for evaluating the KPS.
11 April 2018	To remove the comparative Part 2, which consisted of the comparison of irinotecan liposome injection-containing regimens versus nab-paclitaxel plus gemcitabine and all related information (example, comparison versus nab-paclitaxel plus gemcitabine; reporting groups 1, 2 and 3, randomization). The primary objective was then amended from determination of the Part 2 dose of the triplet combination to determination of the recommended dose of the triplet combination for future development. To add or modify inclusion criteria; To add, remove or modify exclusion criteria; To add clinical data in UGT1A1*28 homozygous participants; To update dose modification rules; To modify granulocyte Colony Stimulating Factors; To specify treatment infusion of 5-FU continued at home; and to remove QTcF assessments and Appendix 5 (QT specific), which were specific to Part 2.

27 September 2019	To provide details following fulfilment of analysis requirements for the primary and/or secondary endpoints. Participants still receiving treatment or being followed for OS could transition to an extension phase of the study, continue to be followed for OS and safety, which was completed once all participants had died, withdrew consent, or were lost to follow-up after two attempts on OS follow-up.

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.

The comparative Part 2 was removed in a protocol amendment, dated 11 April 2018, before it was initiated, as this comparative part of the study is being undertaken as a stand-alone Phase 3 study D-US-60010-001.

Notes: