Clinical trial results:
A randomized, multicenter, parallel-group, Phase III study to compare the efficacy of arfolitixorin versus leucovorin in combination with 5 fluorouracil, oxaliplatin, and bevacizumab in patients with advanced colorectal cancer.

Summary

EudraCT number	2017-004154-41
Trial protocol	SE DE FR AT GR
Global end of trial date	22 November 2022

Results information

Result version number	v1 (current)
This version publication date	12 November 2023
First version publication date	12 November 2023

Trial information

Trial identification

Sponsor protocol code	ISO-CC-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03750786
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Isofol Medical AB (publ)
Sponsor organisation address	Arvid Wallgrens backe 20, Göteborg, Sweden, 41346
Public contact	Karin Gedda, Isofol Medical AB, 46 729945337, karin.gedda@isofolmedical.com
Scientific contact	Roger Tell, Isofol Medical AB, 46 760293911, roger.tell@isofolmedical.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	22 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 November 2022
Global end of trial reached?	Yes
Global end of trial date	22 November 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Overall response rate (ORR)

Protection of trial subjects:

The protocol, ICF, and all patient materials were to be submitted to the IECs/IRBs and Regulatory Authorities for review and approval. Approval of both the protocol and the ICF had to be obtained before any patient was enrolled. Amendments to the protocol were to be submitted for review and approval by the IECs/IRBs and Regulatory Authorities as required by local regulations. All changes to the ICF were to be approved by the IECs/IRBs and Regulatory Authorities; a determination was to be made regarding whether a new consent needed to be obtained from participants who had provided consent using a previously approved ICF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 December 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 95
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	Austria: 30
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 53
Country: Number of subjects enrolled	Greece: 59
Country: Number of subjects enrolled	Canada: 43
Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	Japan: 58
Country: Number of subjects enrolled	United States: 85
Worldwide total number of subjects	490
EEA total number of subjects	272

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)	267
From 65 to 84 years	223
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients ≥18 years with nonresectable, biopsy verified metastatic CRC planned for 1st line therapy with 5-FU, Leucovorin, oxaliplatin and bevacizumab. One measurable site of disease according to RECIST 1.1 criteria (at least 10 mm). Life expectancy >4 months, WHO performance status of 0-1 and adequate haematological, renal and hepatic function.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A

Arm description:

ARFOX (arfolitixorin and 5-FU and oxaliplatin) + bevacizumab

Arm type	Experimental
Investigational medicinal product name	arfolitixorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

120 mg/m2 administered as two rapid IV boluses, 60 mg/m2 each, 30-60 minutes apart

Arm title	Group B

Arm description:

mFOLFOX-6 (Leucovorin and 5-FU and oxaliplatin) + bevacizumab

Arm type	Active comparator
Investigational medicinal product name	Leucovorin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

400 mg/m2 administered as an IV infusion

Number of subjects in period 1	Group A	Group B
Started	245	245
Completed	0	0
Not completed	245	245
Early termination of study	245	245

Baseline characteristics

Reporting groups	
Reporting group title	Group A
Reporting group description:	
ARFOX (arfolitixorin and 5-FU and oxaliplatin) + bevacizumab	
Reporting group title	Group B
Reporting group description:	
mFOLFOX-6 (Leucovorin and 5-FU and oxaliplatin) + bevacizumab	

Reporting group values	Group A	Group B	Total
Number of subjects	245	245	490
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	62.4	62.6	
standard deviation	± 10.5	± 10.7	-
Gender categorical			
Units: Subjects			
Female	83	94	177
Male	162	151	313
Time since initial diagnosis			
Units: Months			
arithmetic mean	9.7	7.7	
standard deviation	± 20.9	± 15.2	-

End points

End points reporting groups

Reporting group title	Group A
Reporting group description:	
ARFOX (arfolitixorin and 5-FU and oxaliplatin) + bevacizumab	
Reporting group title	Group B
Reporting group description:	
mFOLFOX-6 (Leucovorin and 5-FU and oxaliplatin) + bevacizumab	

Primary: Overall response rate

End point title	Overall response rate
End point description:	
Best ORR, defined as the best response recorded from the start of the study treatment until the end of treatment.	
End point type	Primary
End point timeframe:	
Until disease progression	

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	245		
Units: Number of participants				
Complete Response	2	5		
Partial Response	116	116		
Stable Disease	106	86		
Progressive Disease	7	11		
Non-CR/Non-PD	6	3		
No BOR Available	6	18		
Not Evaluable	2	6		

Statistical analyses

Statistical analysis title	Best Overall respons rate
Statistical analysis description:	
Best response recorded from start of the study treatment until end of treatment. All responses was confirmed 8 weeks after onset of response. All assessments, including confirmation of response, was based on BICR. The ORR was analyzed using a Cochran-Mantel-Haenszel test, stratified for the stratification factors used for randomization. The ORR was estimated along with its 95% CI. Since sample-size increase took place, the one-sided significance level for the final analysis of ORR was 0.024.	
Comparison groups	Group A v Group B

Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5749
Method	Cochran-Mantel-Haenszel
Confidence interval	
level	95 %
sides	1-sided

Secondary: Progression free survival

End point title	Progression free survival

End point description:

PFS, defined as the time from randomization to first occurrence of tumor progression based on CT-scans/MRIs.

End point type	Secondary

End point timeframe:

Until disease progression

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	245	245		
Units: month				
median (confidence interval 95%)	12.8 (10.9 to 13.2)	11.6 (11.0 to 14.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

The duration of response is measured from the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented.

End point type	Secondary

End point timeframe:

Until disease progression

End point values	Group A	Group B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	121		
Units: month				
median (confidence interval 95%)	12.2 (11.1 to 14.1)	12.9 (10.6 to 15.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
1 year	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups	
Reporting group title	Group A
Reporting group description: -	
Reporting group title	Group B
Reporting group description: -	

Serious adverse events	Group A	Group B	
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 243 (33.33%)	86 / 238 (36.13%)	
number of deaths (all causes)	118	100	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour perforation			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	2 / 243 (0.82%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (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			
Catheter site extravasation			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	1 / 243 (0.41%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal inflammation			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	6 / 243 (2.47%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	1 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Rectoprostatic fistula			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 243 (0.41%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dyspnoea exertional			

subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	8 / 243 (3.29%)	8 / 238 (3.36%)	
occurrences causally related to treatment / all	1 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	2 / 243 (0.82%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Investigations			
C-reactive protein increased			

subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 243 (0.41%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal anastomotic leak			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 243 (0.41%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			

subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 243 (0.41%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output syndrome			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersomnia			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic encephalopathy			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myoclonus			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	2 / 243 (0.82%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 243 (0.82%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 243 (1.23%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	1 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemolytic anemia			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemoid reaction			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal hernia			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 243 (0.82%)	7 / 238 (2.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	2 / 243 (0.82%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 243 (0.82%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 243 (0.82%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	2 / 243 (0.82%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	6 / 243 (2.47%)	10 / 238 (4.20%)	
occurrences causally related to treatment / all	0 / 7	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	5 / 243 (2.06%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Large intestine perforation			
subjects affected / exposed	3 / 243 (1.23%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			

subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
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 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 243 (0.41%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal perforation			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	3 / 243 (1.23%)	5 / 238 (2.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary fistula			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 243 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portosplenomesenteric venous thrombosis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
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	2 / 243 (0.82%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal colic			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 243 (0.41%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Enterococcal infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			

subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal fistula infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			

subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	3 / 243 (1.23%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 243 (1.23%)	3 / 238 (1.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Urinary tract infection			
subjects affected / exposed	1 / 243 (0.41%)	4 / 238 (1.68%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			

subjects affected / exposed	3 / 243 (1.23%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 243 (1.23%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	1 / 243 (0.41%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urosepsis			
subjects affected / exposed	0 / 243 (0.00%)	2 / 238 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal abscess			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecthyma			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis hyperchloraemic			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 243 (0.00%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			

subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 243 (0.82%)	1 / 238 (0.42%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 243 (0.41%)	0 / 238 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group A	Group B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	239 / 243 (98.35%)	231 / 238 (97.06%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	55 / 243 (22.63%)	60 / 238 (25.21%)	
occurrences (all)	55	60	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	48 / 243 (19.75%)	42 / 238 (17.65%)	
occurrences (all)	48	42	
Fatigue			
subjects affected / exposed	108 / 243 (44.44%)	103 / 238 (43.28%)	
occurrences (all)	108	103	
Malaise			
subjects affected / exposed	13 / 243 (5.35%)	13 / 238 (5.46%)	
occurrences (all)	13	13	
Mucosal inflammation			
subjects affected / exposed	53 / 243 (21.81%)	49 / 238 (20.59%)	
occurrences (all)	53	49	
Oedema peripheral			

subjects affected / exposed	13 / 243 (5.35%)	8 / 238 (3.36%)	
occurrences (all)	13	8	
Pyrexia			
subjects affected / exposed	45 / 243 (18.52%)	39 / 238 (16.39%)	
occurrences (all)	45	39	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	20 / 243 (8.23%)	10 / 238 (4.20%)	
occurrences (all)	20	10	
Dysphonia			
subjects affected / exposed	9 / 243 (3.70%)	22 / 238 (9.24%)	
occurrences (all)	9	22	
Dyspnoea			
subjects affected / exposed	21 / 243 (8.64%)	7 / 238 (2.94%)	
occurrences (all)	21	7	
Epistaxis			
subjects affected / exposed	64 / 243 (26.34%)	62 / 238 (26.05%)	
occurrences (all)	64	62	
Hiccups			
subjects affected / exposed	14 / 243 (5.76%)	14 / 238 (5.88%)	
occurrences (all)	14	14	
Pulmonary embolism			
subjects affected / exposed	21 / 243 (8.64%)	19 / 238 (7.98%)	
occurrences (all)	21	19	
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 243 (2.06%)	13 / 238 (5.46%)	
occurrences (all)	5	13	
Insomnia			
subjects affected / exposed	11 / 243 (4.53%)	18 / 238 (7.56%)	
occurrences (all)	11	18	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	23 / 243 (9.47%)	11 / 238 (4.62%)	
occurrences (all)	23	11	
Aspartate aminotransferase increased			

subjects affected / exposed	22 / 243 (9.05%)	13 / 238 (5.46%)	
occurrences (all)	22	13	
Blood alkaline phosphatase increased			
subjects affected / exposed	9 / 243 (3.70%)	14 / 238 (5.88%)	
occurrences (all)	9	14	
Gamma-glutamyltransferase increased			
subjects affected / exposed	14 / 243 (5.76%)	17 / 238 (7.14%)	
occurrences (all)	14	17	
Neutrophil count decreased			
subjects affected / exposed	53 / 243 (21.81%)	62 / 238 (26.05%)	
occurrences (all)	53	62	
Platelet count decreased			
subjects affected / exposed	33 / 243 (13.58%)	35 / 238 (14.71%)	
occurrences (all)	33	35	
Weight decreased			
subjects affected / exposed	22 / 243 (9.05%)	20 / 238 (8.40%)	
occurrences (all)	22	20	
White blood cell count decreased			
subjects affected / exposed	24 / 243 (9.88%)	25 / 238 (10.50%)	
occurrences (all)	24	25	
Nervous system disorders			
Dizziness			
subjects affected / exposed	23 / 243 (9.47%)	20 / 238 (8.40%)	
occurrences (all)	23	20	
Dysaesthesia			
subjects affected / exposed	26 / 243 (10.70%)	31 / 238 (13.03%)	
occurrences (all)	26	31	
Dysgeusia			
subjects affected / exposed	40 / 243 (16.46%)	37 / 238 (15.55%)	
occurrences (all)	40	37	
Headache			
subjects affected / exposed	25 / 243 (10.29%)	24 / 238 (10.08%)	
occurrences (all)	25	24	
Hypoaesthesia			

subjects affected / exposed	11 / 243 (4.53%)	18 / 238 (7.56%)	
occurrences (all)	11	18	
Neuropathy peripheral			
subjects affected / exposed	73 / 243 (30.04%)	64 / 238 (26.89%)	
occurrences (all)	73	64	
Neurotoxicity			
subjects affected / exposed	40 / 243 (16.46%)	22 / 238 (9.24%)	
occurrences (all)	40	22	
Paraesthesia			
subjects affected / exposed	36 / 243 (14.81%)	42 / 238 (17.65%)	
occurrences (all)	36	42	
Peripheral sensory neuropathy			
subjects affected / exposed	66 / 243 (27.16%)	72 / 238 (30.25%)	
occurrences (all)	66	72	
Polyneuropathy			
subjects affected / exposed	16 / 243 (6.58%)	16 / 238 (6.72%)	
occurrences (all)	16	16	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	44 / 243 (18.11%)	51 / 238 (21.43%)	
occurrences (all)	44	51	
Neutropenia			
subjects affected / exposed	60 / 243 (24.69%)	51 / 238 (21.43%)	
occurrences (all)	60	51	
Thrombocytopenia			
subjects affected / exposed	32 / 243 (13.17%)	28 / 238 (11.76%)	
occurrences (all)	32	28	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	51 / 243 (20.99%)	50 / 238 (21.01%)	
occurrences (all)	51	50	
Abdominal pain upper			
subjects affected / exposed	16 / 243 (6.58%)	14 / 238 (5.88%)	
occurrences (all)	16	14	
Constipation			

subjects affected / exposed	69 / 243 (28.40%)	64 / 238 (26.89%)	
occurrences (all)	69	64	
Diarrhoea			
subjects affected / exposed	118 / 243 (48.56%)	113 / 238 (47.48%)	
occurrences (all)	118	113	
Dyspepsia			
subjects affected / exposed	12 / 243 (4.94%)	23 / 238 (9.66%)	
occurrences (all)	12	23	
Gastrooesophageal reflux disease			
subjects affected / exposed	20 / 243 (8.23%)	12 / 238 (5.04%)	
occurrences (all)	20	12	
Nausea			
subjects affected / exposed	117 / 243 (48.15%)	123 / 238 (51.68%)	
occurrences (all)	117	123	
Stomatitis			
subjects affected / exposed	52 / 243 (21.40%)	62 / 238 (26.05%)	
occurrences (all)	52	62	
Vomiting			
subjects affected / exposed	60 / 243 (24.69%)	55 / 238 (23.11%)	
occurrences (all)	60	55	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	21 / 243 (8.64%)	32 / 238 (13.45%)	
occurrences (all)	21	32	
Dry skin			
subjects affected / exposed	13 / 243 (5.35%)	21 / 238 (8.82%)	
occurrences (all)	13	21	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	20 / 243 (8.23%)	29 / 238 (12.18%)	
occurrences (all)	20	29	
Rash			
subjects affected / exposed	12 / 243 (4.94%)	13 / 238 (5.46%)	
occurrences (all)	12	13	
Renal and urinary disorders			

Proteinuria			
subjects affected / exposed	23 / 243 (9.47%)	13 / 238 (5.46%)	
occurrences (all)	23	13	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 243 (6.17%)	11 / 238 (4.62%)	
occurrences (all)	15	11	
Back pain			
subjects affected / exposed	23 / 243 (9.47%)	25 / 238 (10.50%)	
occurrences (all)	23	25	
Pain in extremity			
subjects affected / exposed	11 / 243 (4.53%)	13 / 238 (5.46%)	
occurrences (all)	11	13	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	24 / 243 (9.88%)	27 / 238 (11.34%)	
occurrences (all)	24	27	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	66 / 243 (27.16%)	60 / 238 (25.21%)	
occurrences (all)	66	60	
Hyperglycaemia			
subjects affected / exposed	6 / 243 (2.47%)	16 / 238 (6.72%)	
occurrences (all)	6	16	
Hypokalaemia			
subjects affected / exposed	18 / 243 (7.41%)	28 / 238 (11.76%)	
occurrences (all)	18	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2019	Amendment 1, dated 29 August 2019, proposed one clarification and two changes to the inclusion/exclusion criteria, the latter in order to align with other studies and with clinical practice. Moreover, it stipulated that oxaliplatin and LV should be administered in sequence or in two different injection ports.
20 February 2020	Amendment 2, dated 20 February 2020, included more information on non-clinical data related to arfolitixorin, the specification of DoR as a secondary endpoint, the inclusion of RFS for patients undergoing metastatic resection as an exploratory endpoint, and several clarifications about data entry, stratification, inclusion criteria, calculation of body surface area, use of bevacizumab biosimilars and further explanations about study treatment, PK sampling, ECG, and the management of patients becoming eligible for metastasis resection. Moreover, the collection of baseline KRAS, BRAF, NRAS mutations was added to the eCRF at screening, when available, to allow for subgroup analyses; the planned OS analysis section was updated following a request from the US Food and Drug Administration; and the work of the DSMB was further detailed, following the decision to follow the recommendation of Japanese authorities regarding the number of patients to be enrolled from Japan.
20 August 2021	Amendment 3, dated 20 August 2021, provided several clarifications, including those about the timing of ORR and PFS analysis, the mechanism of action of arfolitixorin, on the planned PK assessment, on the management of patients with QTcF prolongation, as well as several changes to ensure that the protocol text, the SAP and the DSMB charter were aligned. Moreover, the final list of genes of interest for the pharmacogenetic analyses was provided in this amendment.
22 February 2022	Amendment 4, dated 22 February 2022 was not submitted, and the changes proposed in this amendment were eventually included in protocol version 6.0. The main change was the sample size (from 440 patients to 490 patients, to account for enrollment of additional Japanese patients) and corresponding recruitment period and impact on analysis of ORR, as well as the number of required PFS events (from 300 to 230, see explanation in Section 9.7.1) and expected impact on analysis. Moreover, minor editorial changes were undertaken, and updates were provided in light of the latest version (14.0) of the Investigator's Brochure, the statistical section was updated in accordance with the current version of the SAP, and the phone number for the Sponsor's Chief Medical Officer was updated.
22 April 2022	Amendment 5, dated 22 April 2022, included one additional change to the required number of PFS events (to at least 235, to align with the SAP and with feedback from regulatory authorities), and the inclusion of the ITT excluding additional Japanese patients (ITTE) analysis set, to be in line with the current SAP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported