Clinical trial results:
A Randomized, Double-Blind, Phase 3 Study of the JAK1/2 Inhibitor, Ruxolitinib or Placebo in Combination With Capecitabine in Subjects With Advanced or Metastatic Adenocarcinoma of the Pancreas Who Have Failed or Are Intolerant to First-Line Chemotherapy (The JANUS 1 Study)

Summary

EudraCT number	2014-000293-20
Trial protocol	IT ES BE GB AT
Global end of trial date	22 December 2016

Results information

Result version number	v1 (current)
This version publication date	06 January 2018
First version publication date	06 January 2018

Trial information

Trial identification

Sponsor protocol code	INCB 18424-362

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02117479
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Incyte Corporation
Sponsor organisation address	1801 Augustine Cut-Off, Wilmington, DE, United States, 19803
Public contact	Incyte Corporation, Incyte Corporation Call Centre, +44 (0)330 100 3677, globalmedinfo@incyte.com
Scientific contact	Incyte Corporation, Incyte Corporation Call Centre, +44 (0)330 100 3677, globalmedinfo@incyte.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	20 April 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluate and compare the overall survival (OS) of subjects with advanced or metastatic adenocarcinoma of the pancreas when treated with ruxolitinib in combination with capecitabine versus capecitabine alone.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 March 2014
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	United States: 136
Country: Number of subjects enrolled	Australia: 29
Country: Number of subjects enrolled	New Zealand: 1
Country: Number of subjects enrolled	Taiwan: 20
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	Korea, Republic of: 20
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 15
Worldwide total number of subjects	321
EEA total number of subjects	104

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)	116
From 65 to 84 years	202
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants with advanced or metastatic adenocarcinoma of the pancreas who had failed or were intolerant to first-line chemotherapy were randomized in the study.

Pre-assignment

Screening details:

Treatment was started as soon as possible after randomization (within 3 days) and consisted of continuous 21-day cycles. Capecitabine was self-administered for the first 14 days of each cycle, and ruxolitinib/placebo was self-administered for the entire cycle.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ruxolitinib plus capecitabine

Arm description:

Ruxolitinib 5 mg tablets in combination with Capecitabine 500 mg tablets to be administered by mouth twice daily (BID).

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	Jakafi ®,Jakavi ®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg tablets to be administered by mouth twice daily (BID).

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg tablets to be administered by mouth twice daily (BID).

Arm title	Placebo plus capecitabine

Arm description:

5 mg matching placebo tablets in combination with Capecitabine 500 mg tablets to be administered by mouth twice daily (BID).

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg tablets to be administered by mouth twice daily (BID).

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

500 mg tablets to be administered by mouth twice daily (BID).

Number of subjects in period 1	Ruxolitinib plus capecitabine	Placebo plus capecitabine
Started	161	160
Completed	5	4
Not completed	156	156
Physician decision	7	2
Disease progression	104	108
Other unspecified	11	7
Adverse Event	8	16
Subject decision	8	9
Death	13	8
Noncompliance with study treatment	1	-
Study terminated by the sponsor	4	6

Baseline characteristics

Reporting groups	
Reporting group title	Ruxolitinib plus capecitabine
Reporting group description:	
Ruxolitinib 5 mg tablets in combination with Capecitabine 500 mg tablets to be administered by mouth twice daily (BID).	

Reporting group title	Placebo plus capecitabine
Reporting group description:	
5 mg matching placebo tablets in combination with Capecitabine 500 mg tablets to be administered by mouth twice daily (BID).	

Reporting group values	Ruxolitinib plus capecitabine	Placebo plus capecitabine	Total
Number of subjects	161	160	321
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	54	62	116
From 65-84 years	104	98	202
85 years and over	3	0	3
Age continuous Units: years			
arithmetic mean	67.3	65.6	
standard deviation	± 9.35	± 9.55	-
Gender categorical Units: Subjects			
Female	66	64	130
Male	95	96	191

End points

End points reporting groups

Reporting group title	Ruxolitinib plus capecitabine

Reporting group description:

Ruxolitinib 5 mg tablets in combination with Capecitabine 500 mg tablets to be administered by mouth twice daily (BID).

Reporting group title	Placebo plus capecitabine

Reporting group description:

5 mg matching placebo tablets in combination with Capecitabine 500 mg tablets to be administered by mouth twice daily (BID).

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival is reported here based on the number of deaths from randomization up to 6-months or to the data cutoff 11FEB2016.

End point type	Primary

End point timeframe:

Randomization until death due to any cause; up to the data cutoff 11FEB2016.

End point values	Ruxolitinib plus capecitabine	Placebo plus capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[1]	160[2]		
Units: Count of Participants				
number (not applicable)				
Observed	113	124		
Censored	48	36		

Notes:

[1] - The intent-to-treat (ITT) population consisted of all participants randomized to the study.

[2] - The intent-to-treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

Statistical analysis title	OS: Control vs Active
Comparison groups	Ruxolitinib plus capecitabine v Placebo plus capecitabine

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.969
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.747
upper limit	1.256

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)

End point description:

Progressive Disease (PD) is defined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as at least a 20% increase in the sum of the Longest Diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started, unequivocal progression of non-target lesions, or the appearance of new lesions.
PFS is defined as the time from randomization until the earliest date of disease progression determined by investigator assessment of objective radiographic disease assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause if sooner.

End point type	Secondary

End point timeframe:

Randomization to disease progression, or death due to any cause if sooner; up to 12-months or to the data cutoff 11FEB2016.

End point values	Ruxolitinib plus capecitabine	Placebo plus capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[3]	160[4]		
Units: days				
median (confidence interval 95%)	43.0 (41.0 to 46.0)	44.0 (42.0 to 48.0)		

Notes:

[3] - The intent-to-treat (ITT) population consisted of all participants randomized to the study.

[4] - The intent-to-treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

Statistical analysis title	PFS: Control vs Active
Comparison groups	Ruxolitinib plus capecitabine v Placebo plus capecitabine

Number of subjects included in analysis	321
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.827
upper limit	1.348

Secondary: Proportion of Subjects Progression Free Survival (PFS)

End point title	Proportion of Subjects Progression Free Survival (PFS)

End point description:

Progressive Disease (PD) is defined using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as at least a 20% increase in the sum of the Longest Diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started, unequivocal progression of non-target lesions, or the appearance of new lesions.
PFS is defined as the time from randomization until the earliest date of disease progression determined by investigator assessment of objective radiographic disease assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, or death due to any cause if sooner.

End point type	Secondary

End point timeframe:

Randomization to disease progression, or death due to any cause if sooner; up to 12-months or to the data cutoff 11FEB2016.

End point values	Ruxolitinib plus capecitabine	Placebo plus capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[5]	160[6]		
Units: percentage of participants				
median (confidence interval 95%)				
Survival rate at 3 months	0.189 (0.127 to 0.259)	0.198 (0.136 to 0.268)		
Survival rate at 6 months	0.061 (0.025 to 0.122)	0.057 (0.023 to 0.113)		
Survival rate at 9 months	0.025 (0.005 to 0.075)	0.034 (0.010 to 0.085)		
Survival rate at 12 months	0.025 (0.005 to 0.075)	99.999 (99.999 to 99.999)		

Notes:

[5] - The intent-to-treat (ITT) population consisted of all participants randomized to the study.

[6] - ITT population
99.999= PFS not evaluable due to the insufficient number of participants with events

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective response rate was determined by radiographic disease assessments per RECIST (v1.1), by investigator assessment and was defined as the percentage of participants with Complete Response (CR) or Partial Response (PR) by Response Evaluation Criteria in Solid Tumours (RECIST) at any post baseline visit. Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST) for target lesions and assessed by computed tomography (CT) and/or magnetic resonance imaging (MRI) : Complete Response (CR), Disappearance of all target and non-target lesions and no new lesions; Partial Response (PR), >=30% decrease in the sum of the longest diameter of target lesions with no worsening of non-target lesions; Overall Response (OR) = CR + PR.

End point type	Secondary

End point timeframe:

Baseline through end of study; up to 6-months or to the data cutoff 11FEB2016.

End point values	Ruxolitinib plus capecitabine	Placebo plus capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[7]	160[8]		
Units: percentage of participants				
number (not applicable)				
Objective response	3.7	1.9		
Complete response	0	0		
Partial response	3.7	1.9		

Notes:

[7] - The intent-to-treat (ITT) population consisted of all participants randomized to the study.

[8] - The intent-to-treat (ITT) population consisted of all participants randomized to the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of overall response was defined as the time in months from Complete Response (CR) or Partial Response (PR) by Response Evaluation Criteria in Solid Tumours (RECIST v1.1) until the first date Progressive Disease (PD) was objectively documented or until the date of death.

End point type	Secondary

End point timeframe:

Baseline through end of study; up to 6-months or to the data cutoff 11FEB2016.

End point values	Ruxolitinib plus capecitabine	Placebo plus capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[9]	160[10]		
Units: days				
median (confidence interval 95%)	99.999 (99.999 to 99.999)	99.999 (99.999 to 99.999)		

Notes:

[9] - ITT population:
99.999=DOR not evaluable due to the insufficient number of participants with event
[10] - ITT population:
99.999=DOR not evaluable due to the insufficient number of participants with event

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Rate

End point title	Overall Survival Rate

End point description:

Overall survival rates is reported based on the number of deaths from randomization up to 12-months or to the data cutoff 11FEB2016.

End point type	Secondary

End point timeframe:

Randomization until death due to any cause; up to the data cutoff 11FEB2016.

End point values	Ruxolitinib plus capecitabine	Placebo plus capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	161[11]	160[12]		
Units: percentage of participants				
median (confidence interval 95%)				
Month 3 survival rate	0.498 (0.413 to 0.577)	0.528 (0.443 to 0.605)		
Month 6 survival rate	0.207 (0.135 to 0.289)	0.201 (0.134 to 0.278)		
Month 9 survival rate	0.112 (0.056 to 0.189)	0.062 (0.025 to 0.122)		
Month 12 survival rate	0.053 (0.014 to 0.134)	99.999 (99.999 to 99.999)		

Notes:

[11] - The intent-to-treat (ITT) population consisted of all participants randomized to the study.

[12] - ITT population
99.999= 12-month survival was not evaluable in the placebo group.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study medication through study termination or to the data cutoff 20APR2016.

Adverse event reporting additional description:

The safety evaluable population consisted of all participants exposed to at least 1 dose of study drug (ruxolitinib or placebo).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Ruxolitinib Plus Capecitabine

Reporting group description:

Ruxolitinib 5 mg tablets in combination with Capecitabine 500 mg tablets to be administered by mouth twice daily (BID).

Reporting group title	Placebo Plus Capecitabine

Reporting group description:

5 mg matching placebo tablets in combination with Capecitabine 500 mg tablets to be administered by mouth twice daily (BID).

Serious adverse events	Ruxolitinib Plus Capecitabine	Placebo Plus Capecitabine	
Total subjects affected by serious adverse events			
subjects affected / exposed	98 / 153 (64.05%)	86 / 154 (55.84%)	
number of deaths (all causes)	20	15	
number of deaths resulting from adverse events	2	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	3 / 153 (1.96%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine carcinoma metastatic			

subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	2 / 153 (1.31%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 153 (0.65%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 153 (1.96%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 153 (0.65%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 153 (0.65%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 153 (0.00%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			

subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	3 / 153 (1.96%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	8 / 153 (5.23%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	1 / 8	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 153 (0.65%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	5 / 153 (3.27%)	4 / 154 (2.60%)	
occurrences causally related to treatment / all	1 / 6	0 / 4	
deaths causally related to treatment / all	1 / 1	0 / 0	

Epistaxis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 153 (0.65%)	5 / 154 (3.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	5 / 153 (3.27%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			

subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 153 (1.31%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	4 / 153 (2.61%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			

subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 153 (0.65%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 153 (1.31%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (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 / 153 (0.65%)	0 / 154 (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	2 / 153 (1.31%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Complex regional pain syndrome			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (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	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parkinson's disease			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (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	1 / 153 (0.65%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unresponsive to stimuli			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
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			
Anaemia			
subjects affected / exposed	4 / 153 (2.61%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pancytopenia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
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	6 / 153 (3.92%)	19 / 154 (12.34%)	
occurrences causally related to treatment / all	0 / 6	0 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	6 / 153 (3.92%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 153 (0.65%)	5 / 154 (3.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	5 / 153 (3.27%)	4 / 154 (2.60%)	
occurrences causally related to treatment / all	1 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal obstruction			
subjects affected / exposed	2 / 153 (1.31%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 153 (0.65%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	2 / 153 (1.31%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 153 (0.65%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
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	1 / 153 (0.65%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 153 (0.65%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	4 / 153 (2.61%)	5 / 154 (3.25%)	
occurrences causally related to treatment / all	2 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal haemorrhage			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 153 (0.65%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 153 (1.96%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 153 (0.65%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	7 / 153 (4.58%)	4 / 154 (2.60%)	
occurrences causally related to treatment / all	3 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 153 (0.65%)	4 / 154 (2.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dilatation			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biloma			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	3 / 153 (1.96%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			

subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	3 / 153 (1.96%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
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			
Skin ulcer			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	3 / 153 (1.96%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			

subjects affected / exposed	5 / 153 (3.27%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 153 (0.65%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 153 (0.65%)	3 / 154 (1.95%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Biliary sepsis			
subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	2 / 153 (1.31%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis suppurative			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 153 (1.31%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			

subjects affected / exposed	2 / 153 (1.31%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 153 (2.61%)	8 / 154 (5.19%)	
occurrences causally related to treatment / all	0 / 4	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia klebsiella			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			

subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 153 (3.27%)	5 / 154 (3.25%)	
occurrences causally related to treatment / all	0 / 5	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 153 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin candida			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 153 (1.31%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 153 (1.31%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	8 / 153 (5.23%)	4 / 154 (2.60%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			

subjects affected / exposed	1 / 153 (0.65%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	3 / 153 (1.96%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	3 / 153 (1.96%)	0 / 154 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	3 / 153 (1.96%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 153 (1.31%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	6 / 153 (3.92%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	2 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 153 (0.00%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 153 (0.65%)	0 / 154 (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	Ruxolitinib Plus Capecitabine	Placebo Plus Capecitabine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	146 / 153 (95.42%)	145 / 154 (94.16%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	8 / 153 (5.23%)	3 / 154 (1.95%)	
occurrences (all)	8	3	
Hypertension			
subjects affected / exposed	8 / 153 (5.23%)	3 / 154 (1.95%)	
occurrences (all)	9	3	
Hypotension			
subjects affected / exposed	12 / 153 (7.84%)	8 / 154 (5.19%)	
occurrences (all)	13	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	17 / 153 (11.11%)	18 / 154 (11.69%)	
occurrences (all)	19	23	
Chills			
subjects affected / exposed	8 / 153 (5.23%)	4 / 154 (2.60%)	
occurrences (all)	8	4	
Fatigue			
subjects affected / exposed	48 / 153 (31.37%)	51 / 154 (33.12%)	
occurrences (all)	54	54	
Oedema			
subjects affected / exposed	11 / 153 (7.19%)	3 / 154 (1.95%)	
occurrences (all)	11	4	
Oedema peripheral			
subjects affected / exposed	20 / 153 (13.07%)	35 / 154 (22.73%)	
occurrences (all)	21	35	
Pyrexia			
subjects affected / exposed	27 / 153 (17.65%)	13 / 154 (8.44%)	
occurrences (all)	30	19	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	10 / 153 (6.54%)	13 / 154 (8.44%)	
occurrences (all)	11	13	
Dyspnoea			
subjects affected / exposed	9 / 153 (5.88%)	18 / 154 (11.69%)	
occurrences (all)	10	18	
Hiccups			
subjects affected / exposed	9 / 153 (5.88%)	2 / 154 (1.30%)	
occurrences (all)	9	2	
Pleural effusion			
subjects affected / exposed	9 / 153 (5.88%)	2 / 154 (1.30%)	
occurrences (all)	9	2	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 153 (8.50%)	7 / 154 (4.55%)	
occurrences (all)	13	8	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 153 (5.88%)	4 / 154 (2.60%)	
occurrences (all)	11	4	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 153 (6.54%)	3 / 154 (1.95%)	
occurrences (all)	11	3	
Weight decreased			
subjects affected / exposed	10 / 153 (6.54%)	6 / 154 (3.90%)	
occurrences (all)	11	6	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	11 / 153 (7.19%)	4 / 154 (2.60%)	
occurrences (all)	13	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 153 (12.42%)	12 / 154 (7.79%)	
occurrences (all)	20	13	
Dysgeusia			

subjects affected / exposed	4 / 153 (2.61%)	8 / 154 (5.19%)	
occurrences (all)	4	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	45 / 153 (29.41%)	23 / 154 (14.94%)	
occurrences (all)	63	31	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	16 / 153 (10.46%)	11 / 154 (7.14%)	
occurrences (all)	16	11	
Abdominal pain			
subjects affected / exposed	35 / 153 (22.88%)	43 / 154 (27.92%)	
occurrences (all)	40	48	
Abdominal pain upper			
subjects affected / exposed	13 / 153 (8.50%)	13 / 154 (8.44%)	
occurrences (all)	13	14	
Ascites			
subjects affected / exposed	21 / 153 (13.73%)	19 / 154 (12.34%)	
occurrences (all)	22	21	
Constipation			
subjects affected / exposed	35 / 153 (22.88%)	26 / 154 (16.88%)	
occurrences (all)	36	30	
Diarrhoea			
subjects affected / exposed	41 / 153 (26.80%)	37 / 154 (24.03%)	
occurrences (all)	55	51	
Dry mouth			
subjects affected / exposed	3 / 153 (1.96%)	9 / 154 (5.84%)	
occurrences (all)	3	9	
Flatulence			
subjects affected / exposed	9 / 153 (5.88%)	3 / 154 (1.95%)	
occurrences (all)	9	3	
Nausea			
subjects affected / exposed	46 / 153 (30.07%)	48 / 154 (31.17%)	
occurrences (all)	58	52	
Stomatitis			

subjects affected / exposed	30 / 153 (19.61%)	18 / 154 (11.69%)	
occurrences (all)	32	21	
Vomiting			
subjects affected / exposed	30 / 153 (19.61%)	45 / 154 (29.22%)	
occurrences (all)	49	56	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	38 / 153 (24.84%)	26 / 154 (16.88%)	
occurrences (all)	46	36	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	8 / 153 (5.23%)	4 / 154 (2.60%)	
occurrences (all)	8	4	
Back pain			
subjects affected / exposed	19 / 153 (12.42%)	13 / 154 (8.44%)	
occurrences (all)	19	13	
Muscular weakness			
subjects affected / exposed	8 / 153 (5.23%)	5 / 154 (3.25%)	
occurrences (all)	8	5	
Pain in extremity			
subjects affected / exposed	9 / 153 (5.88%)	2 / 154 (1.30%)	
occurrences (all)	9	2	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	9 / 153 (5.88%)	6 / 154 (3.90%)	
occurrences (all)	15	6	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	31 / 153 (20.26%)	47 / 154 (30.52%)	
occurrences (all)	36	50	
Dehydration			
subjects affected / exposed	10 / 153 (6.54%)	9 / 154 (5.84%)	
occurrences (all)	10	9	
Hyperglycaemia			
subjects affected / exposed	4 / 153 (2.61%)	9 / 154 (5.84%)	
occurrences (all)	12	9	

Hypokalaemia			
subjects affected / exposed	17 / 153 (11.11%)	12 / 154 (7.79%)	
occurrences (all)	21	15	
Hyponatraemia			
subjects affected / exposed	9 / 153 (5.88%)	5 / 154 (3.25%)	
occurrences (all)	11	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 June 2014	The primary purpose of the amendment was to add the exclusion of subjects who had a known hypersensitivity to any of the active substances, including 5-FU, ruxolitinib, or any of their excipients.
23 September 2014	The primary purpose of the amendment was to provide clarification regarding eligibility criteria, the definition of RMST, the alpha-control plan for secondary endpoints, and the administration of capecitabine. Important changes included: • Defining prior systemic and radiation therapy, measurable and evaluable disease at screening, and subjects who were required to use appropriate contraception. • Clarifying exclusions for cardiac disease. • Adding an exclusion for prior treatment with a JAK inhibitor. • Changing RMST from a secondary analysis of the primary endpoint to an alpha controlled secondary endpoint to be tested after the log rank OS analysis in a sequential testing procedure. • Implementing an alternative, less-conservative alpha-spending plan (HSD using parameter - 4) for secondary endpoints to control familywise error at the overall 0.025 (one-sided level) while maintaining the sequential gatekeeping procedure for testing secondary endpoints. Previously, secondary endpoints were to be tested using the same allocation scheme used for the primary endpoint (HSD using parameter -15), which could have unnecessarily reduced power for the secondary endpoints. • Clarifying that the total daily capecitabine dose (2000 mg/m^2) was to be administered in approximately equal doses BID using only 500 mg capecitabine tablets because of concerns associated with intersubject dose variation using 2 different tablet strengths (150 mg and 500 mg).

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 study was terminated as other related studies of ruxolitinib did not provide sufficient efficacy to warrant continuation at the recommendation of the Data Monitoring Committee.

Notes: