



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Capecitabine and Cisplatin With or Without Ramucirumab as First-line Therapy in Patients With Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (RAINFALL)

Summary

EudraCT number	2014-002240-40
Trial protocol	HU DE FI NL IT ES PL BE GB CZ DK
Global end of trial date	14 August 2020

Results information

Result version number	v1 (current)
This version publication date	15 August 2021
First version publication date	15 August 2021

Trial information

Trial identification

Sponsor protocol code	I4T-MC-JVCU
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02314117
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15372

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	14 August 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 August 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the efficacy of ramucirumab, which is a targeted antibody, in combination with capecitabine and cisplatin compared to capecitabine and cisplatin alone in participants with stomach cancer.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 January 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Argentina: 43
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	United States: 73
Country: Number of subjects enrolled	Czechia: 19
Country: Number of subjects enrolled	Japan: 60
Country: Number of subjects enrolled	United Kingdom: 42
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Denmark: 15
Country: Number of subjects enrolled	Poland: 18
Country: Number of subjects enrolled	Italy: 73
Country: Number of subjects enrolled	Mexico: 52

Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	France: 40
Country: Number of subjects enrolled	Germany: 33
Worldwide total number of subjects	645
EEA total number of subjects	284

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)	405
From 65 to 84 years	238
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

Completers are defined as participants who died or those who were alive and off treatment when the study completed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramucirumab + Cisplatin + Capecitabine

Arm description:

8 milligrams/kilogram (mg/kg) ramucirumab given intravenously (IV) on days 1 and 8 in combination with 80 mg/square meter (m²) cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m² capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m²/day fluorouracil (5-FU) IV on days 1 to 5 of each 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab
Investigational medicinal product code	
Other name	LY3009806,IMC-1121B,Cyramza
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV

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

Dosage and administration details:

Administered orally

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use
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Dosage and administration details:

Administered IV

Arm title	Placebo + Cisplatin + Capecitabine
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Arm description:

Placebo for blinding given IV on days 1 and 8 in combination with 80 mg/m² cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m² capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m²/day 5-FU IV on days 1 to 5 of each 21-day cycle.

Arm type	Active comparator
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administered orally

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered IV

Number of subjects in period 1	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine
Started	326	319
Received at least one dose of study drug	323	315
Completed	314	303
Not completed	12	16
Consent withdrawn by subject	3	2

Lost to follow-up	9	14
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Baseline characteristics

Reporting groups

Reporting group title	Ramucirumab + Cisplatin + Capecitabine
Reporting group description:	
8 milligrams/kilogram (mg/kg) ramucirumab given intravenously (IV) on days 1 and 8 in combination with 80 mg/square meter (m ²) cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m ² capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m ² /day fluorouracil (5-FU) IV on days 1 to 5 of each 21-day cycle.	
Reporting group title	Placebo + Cisplatin + Capecitabine
Reporting group description:	
Placebo for blinding given IV on days 1 and 8 in combination with 80 mg/m ² cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m ² capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m ² /day 5-FU IV on days 1 to 5 of each 21-day cycle.	

Reporting group values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine	Total
Number of subjects	326	319	645
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.9	60.1	
standard deviation	± 11.6	± 11.8	-
Gender categorical Units: Subjects			
Female	112	104	216
Male	214	215	429
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	67	62	129
Not Hispanic or Latino	227	245	472
Unknown or Not Reported	32	12	44
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	12	11	23
Asian	38	31	69
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	2	3	5
White	256	264	520
More than one race	0	0	0
Unknown or Not Reported	17	10	27
Region of Enrollment Units: Subjects			
Puerto Rico	1	1	2
Argentina	21	22	43
Hungary	15	16	31

United States	42	31	73
Czechia	11	8	19
Japan	32	28	60
United Kingdom	20	22	42
Russia	25	25	50
Spain	10	13	23
Canada	10	6	16
Netherlands	4	7	11
Belgium	8	5	13
Finland	3	5	8
Denmark	12	3	15
Poland	8	10	18
Italy	28	45	73
Mexico	26	26	52
Israel	11	12	23
France	19	21	40
Germany	20	13	33

End points

End points reporting groups

Reporting group title	Ramucirumab + Cisplatin + Capecitabine
Reporting group description:	
8 milligrams/kilogram (mg/kg) ramucirumab given intravenously (IV) on days 1 and 8 in combination with 80 mg/square meter (m ²) cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m ² capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m ² /day fluorouracil (5-FU) IV on days 1 to 5 of each 21-day cycle.	
Reporting group title	Placebo + Cisplatin + Capecitabine
Reporting group description:	
Placebo for blinding given IV on days 1 and 8 in combination with 80 mg/m ² cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m ² capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m ² /day 5-FU IV on days 1 to 5 of each 21-day cycle.	

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
End point description:	
PFS time was measured from the date of randomization to the date of radiographic(rgr) documentation of progression(by RECIST v.1.1) or the date of death due to any cause, whichever was earlier.If a participant did not have a complete baseline tumor assessment,then the PFS time was censored at the randomization date.If a participant was not known to have died or have rgr documented progression as of the data cutoff date for the analysis, the PFS time was censored at the last adequate tumor assessment date. If death or progressive disease(PD) occurred after 2 or more consecutive missing rgr visits,censoring occurred at the date of the last rgr visit prior to the missed visits.If death or PD occurred after postdiscontinuation(pdis) systemic anticancer therapy,censoring occurred at the date of last rgr visit prior to the start of pdis systemic anticancer therapy. PD was defined according to RECIST v.1.1.	
End point type	Primary
End point timeframe:	
Randomization to Radiological Disease Progression or Death from Any Cause (Up to 26 Months)	
Analysis Population: First 508 randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=87 and Placebo+Cisplatin+Capecitabine=62.	

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	255	253		
Units: months				
median (confidence interval 95%)	5.72 (5.45 to 6.51)	5.39 (4.47 to 5.72)		

Statistical analyses

Statistical analysis title	Progression-free Survival (PFS)
Comparison groups	Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine
Number of subjects included in analysis	508
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.753
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.607
upper limit	0.935

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was time from the date of randomization to the date of death from any cause. If the participant was alive at the cutoff for analysis (or was lost to follow-up), OS data were censored for analysis on the last date the participant was known to be alive.	
Analysis Population Description (APD): All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=87 and Placebo + Cisplatin + Capecitabine=88.	
End point type	Secondary
End point timeframe:	
Randomization to Death from Any Cause (Up To 30 Months)	

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	319		
Units: months				
median (confidence interval 95%)	11.17 (9.92 to 11.93)	10.74 (9.53 to 11.89)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)
Comparison groups	Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine

Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.962
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.801
upper limit	1.156

Secondary: Progression- free Survival 2 (PFS2)

End point title	Progression- free Survival 2 (PFS2)
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End point description:

PFS2 was defined as the time from the date of randomization to second disease progression (defined as objective radiological or symptomatic progression), or death of any cause, whichever occurs first. Participants alive and for whom a second disease progression has not been observed (including participants who did not receive any additional systemic anticancer treatments) were censored at the last time known to be alive and without second disease progression. The second progression refers to disease progression on or after additional systemic anticancer therapy, regardless if any earlier progression is observed or not (e.g. at the end of study treatment). It is assessed by investigator based on overall clinical evaluation, not limited to RECIST.

APD: All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=74 and Placebo + Cisplatin + Capecitabine=74.

End point type	Secondary
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End point timeframe:

Randomization to Second Radiological or Symptomatic Disease Progression After the Start of Additional Systemic Anticancer Treatment or Death from Any Cause (Up To 26 Months)

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	319		
Units: months				
median (confidence interval 95%)	10.18 (9.03 to 10.84)	9.20 (8.34 to 9.99)		

Statistical analyses

Statistical analysis title	Progression- free Survival 2 (PFS2)
Comparison groups	Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine

Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.926
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.774
upper limit	1.108

Secondary: Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Objective Response Rate [ORR])

End point title	Percentage of Participants With Complete Response (CR) or Partial Response (PR) (Objective Response Rate [ORR])
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End point description:

Response was defined using Response Evaluation Criteria In Solid Tumors (RECIST v1.1). Target lesions - CR: Disappearance of all lesions; any pathological lymph nodes must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of lesions vs the baseline sum. PD: At least a 20% increase in the sum of diameters of lesions vs the smallest sum on study (the sum must also demonstrate an absolute increase of at least 5 mm); or the appearance of new lesion(s). Non target lesions - CR: Disappearance of all lesions and normalization of tumor marker levels; all lymph nodes must be non-pathological in size. Non-CR/Non-PD: Persistence of lesion(s) and/or maintenance of abnormal tumor marker levels. PD: Unequivocal progression of existing lesions or the appearance of new lesion(s). ORR calculated as: (sum of the number of participants with PRs and CRs) divided by (number of evaluable participants) multiplied by 100.

APD: All randomized participants.

End point type	Secondary
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End point timeframe:

Randomization to Disease Progression (Up To 26 Months)

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	319		
Units: percentage of participants				
number (confidence interval 95%)	41.1 (35.8 to 46.4)	36.4 (31.1 to 41.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Response (CR), Partial Response (PR) or Stable Disease (SD) (Disease Control Rate [DCR])

End point title	Percentage of Participants With Complete Response (CR), Partial Response (PR) or Stable Disease (SD) (Disease Control
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End point description:

DCR was the percentage of participants with a best overall response of CR, PR, or SD as per Response using RECIST v1.1 criteria. Target lesions - CR: Disappearance of all lesions; any pathological lymph nodes must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of lesions vs the baseline sum. Progressive Disease (PD): At least a 20% increase in the sum of diameters of lesions vs the smallest sum on study (the sum must also demonstrate an absolute increase of at least 5 mm); or the appearance of new lesion(s). Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Non target lesions - CR: Disappearance of all lesions and normalization of tumor marker levels; all lymph nodes must be non-pathological in size. Non-CR/Non-PD: Persistence of lesion(s) and/or maintenance of abnormal tumor marker levels. PD: Unequivocal progression of existing lesions or the appearance of new lesion(s).

End point type	Secondary
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End point timeframe:

Randomization to Disease Progression (Up To 26 Months)

APD: All randomized participants.

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	319		
Units: percentage of participants				
number (confidence interval 95%)	81.9 (77.7 to 86.1)	76.5 (71.8 to 81.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)
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End point description:

TTP was time from the date of randomization to the date of radiographic progression (according to RECIST v.1.1). If a participant died due to any reason without radiographic progression, TTP is censored at the last adequate tumor assessment. Target lesions: Progressive Disease (PD): At least a 20% increase in the sum of diameters of lesions vs the smallest sum on study (the sum must also demonstrate an absolute increase of at least 5 mm); or the appearance of new lesion(s). Non target lesions: PD: Unequivocal progression of existing lesions or the appearance of new lesion(s).

End point type	Secondary
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End point timeframe:

Randomization to Disease Progression (Up To 24 Months)

APD: All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=149 and Placebo + Cisplatin + Capecitabine=111.

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	319		
Units: months				
median (confidence interval 95%)	6.77 (5.88 to 7.66)	5.78 (5.55 to 6.37)		

Statistical analyses

Statistical analysis title	Time to Progression (TTP)
Comparison groups	Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine
Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.699
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.569
upper limit	0.859

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)
End point description:	
<p>Participants achieved an objective response if they had a best overall response of CR or PR. Target lesions- CR: Disappearance of all lesions; any pathological lymph nodes must have reduction in short axis to <10 mm. PR: At least a 30% decrease in the sum of diameters of lesions vs the baseline sum. PD: At least a 20% increase in the sum of diameters of lesions vs the smallest sum on study (the sum must also demonstrate an absolute increase of at least 5 mm); or the appearance of new lesion(s). Non target lesions - CR: Disappearance of all lesions and normalization of tumour marker levels; all lymph nodes must be non-pathological in size. Non-CR/Non-PD: Persistence of lesion(s) and/or maintenance of abnormal tumor marker levels. PD: Unequivocal progression of existing lesions or the appearance of new lesion(s). If a participant was not known to have died or have radiographically documented PD as of the data inclusion cutoff date, DOR was censored at the date of the last adequate tumor assessment.</p>	
End point type	Secondary
End point timeframe:	
Date of Complete Response (CR) or Partial Response (PR) to Date of Objective Disease Progression or Death Due to Any Cause (Up To 26 Months)	
All randomized participants. Censored: Ramucirumab + Cisplatin + Capecitabine = 23 & Placebo + Cisplatin + Capecitabine = 10	

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	116		
Units: months				
median (confidence interval 95%)	5.72 (5.09 to 6.34)	4.27 (3.88 to 4.90)		

Statistical analyses

Statistical analysis title	Duration of Response (DoR)
Comparison groups	Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.657
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.499
upper limit	0.866

Secondary: Time to Deterioration in Quality of Life (QoL) on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) - Global Health Status/ QoL Scale

End point title	Time to Deterioration in Quality of Life (QoL) on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) - Global Health Status/ QoL Scale
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End point description:

Time to sustained deterioration was defined as time from randomization to first worsening in QoL with no subsequent non-worsened assessment. Worsening in global health status/QoL was defined as a decrease of ≥ 10 points on a 100-point scale. If a participant did not report worsening, time to sustained deterioration was censored at date of last non-worsened assessment.

APD: All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=215 and Placebo + Cisplatin + Capecitabine=217.

End point type	Secondary
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End point timeframe:

Randomization, First worsening in QoL (Up To 26 Months)

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326	319		
Units: months				
median (confidence interval 95%)	9.00 (8.08 to 12.58)	9.46 (6.74 to 11.99)		

Statistical analyses

Statistical analysis title	Time to Deterioration in Quality of Life (QoL)
Comparison groups	Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine
Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.013
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.332

Secondary: Change in Health Status on the EuroQol 5-Dimensions 5-Level Instrument (EQ-5D- 5L)

End point title	Change in Health Status on the EuroQol 5-Dimensions 5-Level Instrument (EQ-5D- 5L)
End point description:	<p>The EQ-5D-5L is a standardized instrument for use as a measure of self-reported health status. Five dimensions of health status are each assessed with 5 response options and scored as a composite index which were anchored on a scale of 0 to 1 with a higher score representing better health status. Additionally, current health status was assessed on a visual analogue scale (VAS) ranging from 0 to 100 with a higher score representing better health status.</p> <p>APD: All randomized participants who provided data at baseline and cycle 6.</p>
End point type	Secondary
End point timeframe:	Randomization, 30 Days After Treatment Discontinuation (Up To 5 Months)

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	125		
Units: units on a scale				
arithmetic mean (standard deviation)				

EQ-5D index	-0.008 (± 0.148)	-0.010 (± 0.157)		
EQ-5D VAS	0.8 (± 18.56)	1.5 (± 20.33)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

End point title	Time to Deterioration in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)
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End point description:

The time from the date of randomization to the first date observing ECOG PS ≥ 2 (that is, deterioration from baseline status of 0 or 1). Participants without PS deterioration were censored at their last documented assessments of 0 or 1. ECOG Performance Status: 2- Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours, 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours, 4 -Completely disabled. Cannot carry on any selfcare.Totally confined to bed or chair,5- Dead.

APD: All randomized participants. Participants censored: Ramucirumab + Cisplatin + Capecitabine=254 and Placebo + Cisplatin + Capecitabine= 260.

End point type	Secondary
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End point timeframe:

Randomization to ECOG PS ≥ 2 (Up To 26 Months)

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	326 ^[1]	319 ^[2]		
Units: months				
median (confidence interval 95%)	999 (12.2 to 999)	999 (999 to 999)		

Notes:

[1] - 999=NA.

Very few events occurred therefore data were not assessable.

[2] - 999=NA

Very few events occurred therefore data were not assessable.

Statistical analyses

Statistical analysis title	Time to Deterioration ECOG and PS
Comparison groups	Ramucirumab + Cisplatin + Capecitabine v Placebo + Cisplatin + Capecitabine
Number of subjects included in analysis	645
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.117

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.58

Secondary: Number of Participants with Anti-Ramucirumab Antibodies

End point title	Number of Participants with Anti-Ramucirumab Antibodies
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End point description:

Participants who developed treatment-emergent antibody responses to Ramucirumab postbaseline.

Analysis Population Description: All participants who received at least one dose of study drug.

End point type	Secondary
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End point timeframe:

Predose Cycle 1 through 30 Days After Treatment Discontinuation (Up To 24 Months)

End point values	Ramucirumab + Cisplatin + Capecitabine	Placebo + Cisplatin + Capecitabine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	315		
Units: participants	4	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Maximum Observed Drug Concentration (Cmax) of Ramucirumab

End point title	Pharmacokinetics (PK): Maximum Observed Drug Concentration (Cmax) of Ramucirumab ^[3]
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End point description:

Pharmacokinetics (PK): Pharmacokinetics (PK): Maximum Observed Drug Concentration (Cmax) of Ramucirumab

APD: All randomized participants who received ramucirumab and had evaluable PK data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1: 1 hour (hr) end of infusion (EOI), Cycle 3 Day 1: 1hr EOI, Cycle 9 Day 1: 1 hr EOI

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK analysis were only planned for experimental arm Ramucirumab + Cisplatin + Capecitabine.

End point values	Ramucirumab + Cisplatin + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	283			
Units: Microgram/milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1	133 (± 31)			
Cycle 3, Day 1	173 (± 35)			
Cycle 9, Day 1	169 (± 60)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Minimum Concentration (Cmin) of Ramucirumab

End point title	PK: Minimum Concentration (Cmin) of Ramucirumab ^[4]
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End point description:

Pharmacokinetics (PK): Minimum Concentration (Cmin) of Ramucirumab

APD: All randomized participants who received ramucirumab and had evaluable PK data.

End point type	Secondary
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End point timeframe:

Cycle 1 Day 1: 1 hour (hr) end of infusion (EOI), Cycle 3 Day 1: 1hr EOI, Cycle 9 Day 1: 1 hr EOI

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK analysis were only planned for experimental arm Ramucirumab + Cisplatin + Capecitabine.

End point values	Ramucirumab + Cisplatin + Capecitabine			
Subject group type	Reporting group			
Number of subjects analysed	268			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 8	40.7 (± 35)			
Cycle 2, Day 1	35.7 (± 56)			
Cycle 3, Day 1	51.2 (± 47)			
Cycle 5, Day 1	69.7 (± 52)			
Cycle 9, Day 1	77.6 (± 98)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline Up to 5.6 Years

Adverse event reporting additional description:

All participants who received at least one dose of study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.0
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Reporting groups

Reporting group title	Placebo+Capecitabine+Cisplatin
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Reporting group description:

Placebo for blinding given IV on days 1 and 8 in combination with 80 mg/m² cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m² capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m²/day 5-FU IV on days 1 to 5 of each 21-day cycle.

Reporting group title	LY3009806+Capecitabine+Cisplatin
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Reporting group description:

8 milligrams/kilogram (mg/kg) ramucirumab given intravenously (IV) on days 1 and 8 in combination with 80 mg/square meter (m²) cisplatin given IV on day 1 of each 21-day cycle (for up to 6 cycles) and 1000 mg/m² capecitabine given orally twice a day on days 1 through 14. Participants that were unable to take capecitabine will be given 800 mg/m²/day fluorouracil (5-FU) IV on days 1 to 5 of each 21-day cycle.

Serious adverse events	Placebo+Capecitabine+Cisplatin	LY3009806+Capecitabine+Cisplatin	
Total subjects affected by serious adverse events			
subjects affected / exposed	150 / 315 (47.62%)	161 / 323 (49.85%)	
number of deaths (all causes)	21	19	
number of deaths resulting from adverse events	8	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
colorectal cancer			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
malignant pleural effusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

metastases to peritoneum alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour associated fever alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tumour haemorrhage alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
arterial thrombosis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
brachiocephalic vein thrombosis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
circulatory collapse alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
deep vein thrombosis alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	3 / 315 (0.95%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	3 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
embolism arterial			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
embolism venous			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypotension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 315 (0.95%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypovolaemic shock			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
orthostatic hypotension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

phlebitis deep alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 315 (0.00%) 0 / 0 0 / 0	1 / 323 (0.31%) 0 / 1 0 / 0	
subclavian vein thrombosis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 315 (0.32%) 2 / 2 0 / 0	0 / 323 (0.00%) 0 / 0 0 / 0	
thrombophlebitis superficial alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 315 (0.32%) 1 / 1 0 / 0	0 / 323 (0.00%) 0 / 0 0 / 0	
venous thrombosis alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 315 (0.00%) 0 / 0 0 / 0	1 / 323 (0.31%) 1 / 1 0 / 0	
venous thrombosis limb alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 315 (0.32%) 0 / 1 0 / 0	0 / 323 (0.00%) 0 / 0 0 / 0	
General disorders and administration site conditions asthenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 315 (0.63%) 2 / 2 0 / 0	3 / 323 (0.93%) 3 / 3 0 / 0	
complication associated with device alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
death			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
device occlusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fall			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
fatigue			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 315 (0.95%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 315 (1.59%)	6 / 323 (1.86%)	
occurrences causally related to treatment / all	4 / 5	2 / 7	
deaths causally related to treatment / all	0 / 1	0 / 1	
heparin-induced thrombocytopenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

impaired healing				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
infusion related reaction				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
malaise				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	1 / 315 (0.32%)	3 / 323 (0.93%)		
occurrences causally related to treatment / all	1 / 1	1 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
mucosal inflammation				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	2 / 315 (0.63%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	2 / 2	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
multiple organ dysfunction syndrome				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	3 / 315 (0.95%)	0 / 323 (0.00%)		
occurrences causally related to treatment / all	2 / 4	0 / 0		
deaths causally related to treatment / all	2 / 3	0 / 0		
non-cardiac chest pain				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	2 / 315 (0.63%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
pain				
alternative dictionary used: MedDRA 23.0				

subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyrexia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	12 / 315 (3.81%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	3 / 12	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
sudden death			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
dyspnoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
hiccups			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoxia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 315 (0.95%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia aspiration			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

pneumothorax spontaneous alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 315 (0.00%) 0 / 0 0 / 0	1 / 323 (0.31%) 0 / 1 0 / 0	
pulmonary embolism alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	9 / 315 (2.86%) 7 / 9 2 / 2	7 / 323 (2.17%) 5 / 7 0 / 1	
respiratory failure alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 315 (0.00%) 0 / 0 0 / 0	1 / 323 (0.31%) 1 / 1 0 / 0	
Psychiatric disorders confusional state alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 315 (0.63%) 0 / 2 0 / 0	1 / 323 (0.31%) 0 / 1 0 / 0	
delirium alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 315 (0.32%) 1 / 1 0 / 0	1 / 323 (0.31%) 2 / 2 0 / 0	
depression alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 315 (0.32%) 0 / 1 0 / 0	0 / 323 (0.00%) 0 / 0 0 / 0	
Investigations alanine aminotransferase increased alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood bilirubin increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood creatinine increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
blood potassium decreased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
body temperature increased			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
creatinine renal clearance decreased			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutrophil count decreased alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
platelet count decreased alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
weight decreased alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (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 alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
accidental overdose alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
device dislocation alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	3 / 315 (0.95%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal stoma complication alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin laceration alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vascular access complication alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
acute myocardial infarction alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
angina pectoris alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
arrhythmia alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
arrhythmia supraventricular alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
atrial fibrillation alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	2 / 315 (0.63%)	2 / 323 (0.62%)		
occurrences causally related to treatment / all	0 / 2	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
atrioventricular block complete alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
cardiac arrest alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	1 / 1		
cardiac disorder alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
cardiogenic shock alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		

pericardial effusion			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sinus bradycardia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
sinus node dysfunction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
supraventricular extrasystoles			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tachycardia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebral infarction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebrovascular accident			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	3 / 315 (0.95%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
cognitive disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhage intracranial			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ischaemic stroke			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nervous system disorder			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
presyncope			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

syncope alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 315 (0.32%) 0 / 1 0 / 0	 2 / 323 (0.62%) 0 / 2 0 / 0	
Blood and lymphatic system disorders anaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 11 / 315 (3.49%) 13 / 16 0 / 0	 11 / 323 (3.41%) 5 / 11 0 / 0	
blood loss anaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 315 (0.32%) 0 / 3 0 / 0	 0 / 323 (0.00%) 0 / 0 0 / 0	
bone marrow failure alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 315 (0.32%) 0 / 1 0 / 0	 1 / 323 (0.31%) 2 / 2 0 / 0	
febrile neutropenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 11 / 315 (3.49%) 12 / 13 0 / 0	 5 / 323 (1.55%) 5 / 5 0 / 0	
haemolytic anaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 315 (0.32%) 0 / 1 0 / 1	 0 / 323 (0.00%) 0 / 0 0 / 0	
leukopenia alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	8 / 315 (2.54%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	9 / 9	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancytopenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombocytopenia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
retinal vein thrombosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	7 / 315 (2.22%)	13 / 323 (4.02%)	
occurrences causally related to treatment / all	0 / 10	3 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal pain upper			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal rigidity			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute abdomen			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ascites			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 315 (0.95%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
constipation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

diarrhoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	19 / 315 (6.03%)	11 / 323 (3.41%)	
occurrences causally related to treatment / all	16 / 20	10 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
dysphagia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	7 / 315 (2.22%)	8 / 323 (2.48%)	
occurrences causally related to treatment / all	0 / 8	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
enteritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterocolitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterocutaneous fistula			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
erosive oesophagitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric haemorrhage			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	3 / 315 (0.95%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	1 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
gastric perforation alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	9 / 323 (2.79%)	
occurrences causally related to treatment / all	1 / 1	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric ulcer haemorrhage alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric ulcer perforation alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal haemorrhage alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastrointestinal obstruction alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haematemesis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 315 (0.95%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

haematochezia				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
hiatus hernia				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
ileus				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	3 / 315 (0.95%)	2 / 323 (0.62%)		
occurrences causally related to treatment / all	0 / 5	0 / 3		
deaths causally related to treatment / all	0 / 1	0 / 1		
ileus paralytic				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
impaired gastric emptying				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
inguinal hernia				
alternative dictionary used: MedDRA 23.0				
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)		
occurrences causally related to treatment / all	0 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
intestinal obstruction				
alternative dictionary used: MedDRA 23.0				

subjects affected / exposed	0 / 315 (0.00%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
intestinal perforation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
intra-abdominal haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
large intestinal stenosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
large intestine perforation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
melaena			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

nausea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	8 / 315 (2.54%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	9 / 10	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
obstruction gastric			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal fistula			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal haemorrhage			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophageal stenosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumoperitoneum			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal haemorrhage			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal obstruction alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal perforation alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
stomatitis alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
subileus alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper gastrointestinal haemorrhage alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	3 / 323 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	22 / 315 (6.98%)	14 / 323 (4.33%)	
occurrences causally related to treatment / all	20 / 27	9 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
bile duct obstruction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholangitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic failure			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 315 (0.95%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
hyperbilirubinaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
dermatomyositis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
palmar-plantar erythrodysaesthesia syndrome			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin disorder			

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	8 / 315 (2.54%)	10 / 323 (3.10%)	
occurrences causally related to treatment / all	10 / 13	8 / 10	
deaths causally related to treatment / all	0 / 1	1 / 2	
hydronephrosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
nephritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nephropathy			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
proteinuria			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyelocaliectasis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal colic			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal impairment			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary retention			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract obstruction			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteonecrosis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
biliary tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cystitis bacterial			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
device related sepsis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterocolitis infectious			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	2 / 323 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
lower respiratory tract infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
periodontitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
periorbital infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

peritonitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
pharyngitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	7 / 315 (2.22%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	0 / 7	1 / 5	
deaths causally related to treatment / all	0 / 3	0 / 0	
pneumonia bacterial			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pseudomembranous colitis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pseudomonas infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyelonephritis			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	5 / 315 (1.59%)	4 / 323 (1.24%)	
occurrences causally related to treatment / all	3 / 5	2 / 5	
deaths causally related to treatment / all	1 / 1	0 / 1	
septic shock			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
vascular device infection			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
cachexia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	0 / 315 (0.00%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
decreased appetite			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	3 / 315 (0.95%)	5 / 323 (1.55%)	
occurrences causally related to treatment / all	1 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	9 / 315 (2.86%)	7 / 323 (2.17%)	
occurrences causally related to treatment / all	4 / 9	4 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
hypercalcaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperglycaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperkalaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	4 / 315 (1.27%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	5 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypomagnesaemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

hyponatraemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	2 / 315 (0.63%)	6 / 323 (1.86%)	
occurrences causally related to treatment / all	2 / 2	8 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypophosphataemia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	0 / 323 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
malnutrition			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	1 / 315 (0.32%)	1 / 323 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo+Capecitabine+Cisplatin	LY3009806+Capecitabine+Cisplatin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	304 / 315 (96.51%)	315 / 323 (97.52%)	
Vascular disorders			
embolism venous			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	17 / 315 (5.40%)	13 / 323 (4.02%)	
occurrences (all)	17	13	
hypertension			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	23 / 315 (7.30%)	70 / 323 (21.67%)	
occurrences (all)	30	152	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed	40 / 315 (12.70%)	44 / 323 (13.62%)	
occurrences (all)	101	133	
fatigue			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	145 / 315 (46.03%)	153 / 323 (47.37%)	
occurrences (all)	309	316	
mucosal inflammation			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	17 / 315 (5.40%)	20 / 323 (6.19%)	
occurrences (all)	41	31	
oedema peripheral			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	33 / 315 (10.48%)	45 / 323 (13.93%)	
occurrences (all)	46	65	
pyrexia			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	40 / 315 (12.70%)	28 / 323 (8.67%)	
occurrences (all)	56	37	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	18 / 315 (5.71%)	25 / 323 (7.74%)	
occurrences (all)	18	29	
dyspnoea			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	21 / 315 (6.67%)	36 / 323 (11.15%)	
occurrences (all)	26	49	
epistaxis			
alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	14 / 315 (4.44%)	48 / 323 (14.86%)	
occurrences (all)	19	76	
hiccups			
alternative dictionary used: MedDRA 23.0			

subjects affected / exposed occurrences (all)	33 / 315 (10.48%) 46	36 / 323 (11.15%) 63	
Psychiatric disorders insomnia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	25 / 315 (7.94%) 27	27 / 323 (8.36%) 29	
Investigations alanine aminotransferase increased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	10 / 315 (3.17%) 15	19 / 323 (5.88%) 29	
aspartate aminotransferase increased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	12 / 315 (3.81%) 17	20 / 323 (6.19%) 25	
blood creatinine increased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	28 / 315 (8.89%) 41	31 / 323 (9.60%) 60	
neutrophil count decreased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	92 / 315 (29.21%) 263	103 / 323 (31.89%) 295	
platelet count decreased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	33 / 315 (10.48%) 75	72 / 323 (22.29%) 254	
weight decreased alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	37 / 315 (11.75%) 56	54 / 323 (16.72%) 72	
white blood cell count decreased alternative dictionary used: MedDRA 23.0			

subjects affected / exposed occurrences (all)	32 / 315 (10.16%) 109	37 / 323 (11.46%) 118	
Nervous system disorders			
dysgeusia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	27 / 315 (8.57%) 31	34 / 323 (10.53%) 38	
dizziness alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	35 / 315 (11.11%) 52	36 / 323 (11.15%) 42	
headache alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	27 / 315 (8.57%) 36	43 / 323 (13.31%) 57	
neuropathy peripheral alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	8 / 315 (2.54%) 9	20 / 323 (6.19%) 30	
peripheral sensory neuropathy alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	31 / 315 (9.84%) 41	39 / 323 (12.07%) 62	
Blood and lymphatic system disorders			
anaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	114 / 315 (36.19%) 289	104 / 323 (32.20%) 276	
neutropenia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	74 / 315 (23.49%) 133	71 / 323 (21.98%) 218	
thrombocytopenia alternative dictionary used: MedDRA 23.0			

subjects affected / exposed occurrences (all)	26 / 315 (8.25%) 51	41 / 323 (12.69%) 106	
Ear and labyrinth disorders tinnitus alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	27 / 315 (8.57%) 32	23 / 323 (7.12%) 26	
Gastrointestinal disorders abdominal pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) abdominal pain upper alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) constipation alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) diarrhoea alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) dyspepsia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) dysphagia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) nausea alternative dictionary used: MedDRA 23.0	51 / 315 (16.19%) 69 15 / 315 (4.76%) 22 78 / 315 (24.76%) 107 107 / 315 (33.97%) 175 12 / 315 (3.81%) 14 17 / 315 (5.40%) 23	52 / 323 (16.10%) 80 22 / 323 (6.81%) 27 104 / 323 (32.20%) 161 108 / 323 (33.44%) 175 19 / 323 (5.88%) 20 21 / 323 (6.50%) 33	

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>stomatitis</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>vomiting</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>186 / 315 (59.05%)</p> <p>444</p> <p>39 / 315 (12.38%)</p> <p>64</p> <p>117 / 315 (37.14%)</p> <p>217</p>	<p>205 / 323 (63.47%)</p> <p>459</p> <p>67 / 323 (20.74%)</p> <p>110</p> <p>134 / 323 (41.49%)</p> <p>249</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>alopecia</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dry skin</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>palmar-plantar erythrodysaesthesia syndrome</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>skin hyperpigmentation</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>16 / 315 (5.08%)</p> <p>20</p> <p>16 / 315 (5.08%)</p> <p>17</p> <p>63 / 315 (20.00%)</p> <p>121</p> <p>10 / 315 (3.17%)</p> <p>10</p>	<p>19 / 323 (5.88%)</p> <p>21</p> <p>20 / 323 (6.19%)</p> <p>23</p> <p>99 / 323 (30.65%)</p> <p>248</p> <p>18 / 323 (5.57%)</p> <p>18</p>	
<p>Renal and urinary disorders</p> <p>proteinuria</p> <p>alternative dictionary used: MedDRA 23.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>36 / 315 (11.43%)</p> <p>60</p>	<p>64 / 323 (19.81%)</p> <p>156</p>	
Musculoskeletal and connective tissue disorders			

back pain alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	16 / 315 (5.08%) 20	28 / 323 (8.67%) 33	
Infections and infestations upper respiratory tract infection alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all)	17 / 315 (5.40%) 18	8 / 323 (2.48%) 11	
Metabolism and nutrition disorders decreased appetite alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) dehydration alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) hypoalbuminaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) hypocalcaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) hypokalaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) hypomagnesaemia alternative dictionary used: MedDRA 23.0 subjects affected / exposed occurrences (all) hyponatraemia	100 / 315 (31.75%) 190 25 / 315 (7.94%) 30 13 / 315 (4.13%) 21 11 / 315 (3.49%) 21 40 / 315 (12.70%) 68 45 / 315 (14.29%) 97	130 / 323 (40.25%) 245 19 / 323 (5.88%) 25 17 / 323 (5.26%) 28 20 / 323 (6.19%) 23 36 / 323 (11.15%) 51 36 / 323 (11.15%) 47	

alternative dictionary used: MedDRA 23.0			
subjects affected / exposed	17 / 315 (5.40%)	18 / 323 (5.57%)	
occurrences (all)	21	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported