Clinical trial results:
A Multicenter, Multinational, Randomized, Double-Blind, Phase III Study of IMC-1121B Plus Docetaxel Versus Placebo Plus Docetaxel in Previously Untreated Patients with HER2-Negative, Unresectable, Locally-Recurrent or Metastatic Breast Cancer

Summary

EudraCT number	2008-001727-65
Trial protocol	ES DE BE CZ SK PL GB GR IE
Global end of trial date	19 November 2020

Results information

Result version number	v2 (current)
This version publication date	11 March 2022
First version publication date	20 November 2021
Version creation reason	• New data added to full data set New data added to full data set

Trial information

Trial identification

Sponsor protocol code	I4T-IE-JVBC

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00703326
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 13892

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	19 November 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to compare the progression-free survival (PFS) of the drug combination ramucirumab plus docetaxel to placebo plus docetaxel in previously untreated participants with human epidermal growth factor receptor 2 (HER2)-negative, unresectable, locally-recurrent or metastatic breast 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	06 August 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 49
Country: Number of subjects enrolled	Brazil: 50
Country: Number of subjects enrolled	Canada: 129
Country: Number of subjects enrolled	Egypt: 12
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Korea, Republic of: 21
Country: Number of subjects enrolled	Lebanon: 38
Country: Number of subjects enrolled	New Zealand: 11
Country: Number of subjects enrolled	Peru: 16
Country: Number of subjects enrolled	Russian Federation: 309
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	South Africa: 63
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	United States: 79
Country: Number of subjects enrolled	Belgium: 68
Country: Number of subjects enrolled	Germany: 17
Country: Number of subjects enrolled	Ireland: 10
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Slovakia: 4

Country: Number of subjects enrolled	Spain: 182
Country: Number of subjects enrolled	Czechia: 7
Country: Number of subjects enrolled	United Kingdom: 31
Worldwide total number of subjects	1144
EEA total number of subjects	305

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)	954
From 65 to 84 years	190
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Not Applicable

Pre-assignment

Screening details:

Participants who were alive and completed the follow-up period or who died were considered to have completed the study.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Ramucirumab (IMC-1121B) + Docetaxel

Arm description:

Ramucirumab (IMC-1121B) is administered at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	Ramucirumab (IMC-1121B)
Investigational medicinal product code	
Other name	IMC-1121B,LY3009806
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ramucirumab (IMC-1121B) is administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

Arm title	Placebo + Docetaxel

Arm description:

Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

Arm type	Placebo
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

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

Dosage and administration details:

Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

Number of subjects in period 1	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel
Started	759	385
Received at least 1 dose of study drug	752	382
Completed	657	347
Not completed	102	38
Consent withdrawn by subject	54	20
Adverse event, non-fatal	1	-
Lost to follow-up	47	18

Baseline characteristics

Reporting groups	
Reporting group title	Ramucirumab (IMC-1121B) + Docetaxel
Reporting group description:	
Ramucirumab (IMC-1121B) is administered at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.	
Reporting group title	Placebo + Docetaxel
Reporting group description:	
Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.	

Reporting group values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel	Total
Number of subjects	759	385	1144
Age categorical Units: Subjects			
Age continuous			
Intent-to-Treat (ITT) Population: All randomized participants.			
Units: years			
arithmetic mean	53.9	54.2	
standard deviation	± 10.5	± 10.0	-
Gender categorical			
Intent-to-Treat (ITT) Population: All randomized participants.			
Units: Subjects			
Female	759	385	1144
Male	0	0	0
Ethnicity (NIH/OMB)			
Intent-to-Treat (ITT) Population: All randomized participants.			
Units: Subjects			
Hispanic or Latino	69	42	111
Not Hispanic or Latino	690	343	1033
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Serbia	0	2	2
United States	58	21	79
Taiwan	4	2	6
Slovakia	2	2	4
Spain	118	64	182
Lebanon	24	14	38
Ireland	8	2	10
Russian Federation	210	99	309
Israel	16	7	23
United Kingdom	21	10	31
Egypt	9	3	12
Czech Republic	4	3	7

Canada	83	46	129
Poland	12	5	17
Belgium	48	20	68
Brazil	30	20	50
Peru	12	4	16
Australia	28	21	49
South Africa	41	22	63
Germany	12	5	17
New Zealand	5	6	11
South Korea	14	7	21
Race			
Intent-to-Treat (ITT) Population: All randomized participants.			
Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	31	20	51
Native Hawaiian or Other Pacific Islander	2	0	2
Black or African American	27	14	41
White	676	341	1017
Other	22	9	31

End points

End points reporting groups

Reporting group title	Ramucirumab (IMC-1121B) + Docetaxel

Reporting group description:

Ramucirumab (IMC-1121B) is administered at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

Reporting group title	Placebo + Docetaxel

Reporting group description:

Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS defined as time from randomization until the first evidence of progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.0) or death from any cause; by Investigator assessment. Progressive disease (PD) defined as at least a 20% increase in sum of longest diameter of target lesions taking as reference the smallest sum longest diameter since baseline, progression in non-target lesions or the appearance of 1 or more new lesion(s). Participants who neither progressed nor died were censored the day of their last radiographic tumor assessment if available or date of randomization if no post initiation radiographic assessment was available. If death or PD occurred after ≥2 missing radiographic visits, censoring occurred at date of last radiographic visit prior to the missed visits.The symptomatic/clinical disease progression (deterioration) without documented radiologic progression did not constitute progression. Censored participants: ramucirumab + docetaxel=94.

End point type	Primary

End point timeframe:

Randomization to disease progression or death or until data cutoff of 31 Mar 2013 (up to 56 months)

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	759[1]	385[2]		
Units: months				
median (confidence interval 95%)	9.5 (8.3 to 9.8)	8.2 (7.1 to 8.5)		

Notes:

[1] - Intent-to-Treat (ITT) Population: All randomized participants.

[2] - Intent-to-Treat (ITT) Population: All randomized participants.

Statistical analyses

Statistical analysis title	Progression-Free Survival (PFS)

Statistical analysis description:

Hazard ratio (HR) with 95% confidence interval (CI) was estimated using a stratified Cox proportional hazards regression model using the Interactive Web Response System (IWRS) stratification factors.

Comparison groups	Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	1144
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.077 [4]
Method	Stratified Log Rank (SLR)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.01

Notes:

[3] - Analysis type: Superiority or Other (legacy)

[4] - SLR used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the duration from randomization to death from any cause. Participants who were alive at data cut-off for the OS analysis or lost to follow-up were censored on the last date the participant was known to be alive. Censored participants: ramucirumab + docetaxel=267, placebo + docetaxel=121.

End point type	Secondary

End point timeframe:

Randomization to death or until data cutoff of 29-May-2015 (up to 82 months)

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	759[5]	385[6]		
Units: months				
median (confidence interval 95%)	30.3 (27.5 to 33.5)	28.7 (25.6 to 32.3)		

Notes:

[5] - Intent-to-Treat (ITT) Population: All randomized participants.

[6] - Intent-to-Treat (ITT) Population: All randomized participants.

Statistical analyses

Statistical analysis title	Overall Survival (OS)

Statistical analysis description:

SLR used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions. HR with 95% confidence interval (CI) was estimated using a stratified Cox proportional hazards regression model using the IWRS stratification factors.

Comparison groups	Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	1144
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.487 [8]
Method	Stratified Log Rank (SLR)
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.1

Notes:

[7] - Superiority or Other (legacy)

[8] - The gate-keeping strategy used to control overall type 1 error 0.05 (2-sided) or 0.025 (1-sided) to analyze progression-free survival (PFS) and OS. At final PFS analysis only if primary PFS test was significant would analysis of OS be inferential.

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

TTP was defined as time from the date of randomization to first documented date of disease progression using Response Evaluation Criteria in Solid Tumors (RECIST v1.0) criteria; by Investigator assessment. Progressive disease (PD) was defined as at least a 20% increase in sum of longest diameter (LD) of target lesions taking as reference smallest sum LD since baseline, progression in non-target lesions or the appearance of 1 or more new lesion(s). Participants who did not progress were censored at the last radiographic tumor assessment. If no post-baseline assessment was available censoring occurred at the date of randomization. If PD occurred after 2 or more missing radiographic visits, censoring occurred at the date of the last radiographic visit prior to the missed visits. The symptomatic/clinical disease progression (deterioration) without documented radiologic progression did not constitute progression. Censored participants: ramucirumab + docetaxel=263, placebo + docetaxel=104.

End point type	Secondary

End point timeframe:

Randomization to disease progression or until data cutoff of 31-Mar-2013 (up to 56 months)

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	759[9]	385[10]		
Units: months				
median (confidence interval 95%)	11.4 (10.7 to 13.3)	9.7 (8.2 to 10.9)		

Notes:

[9] - Intent-to-Treat (ITT) Population: All randomized participants.

[10] - Intent-to-Treat (ITT) Population: All randomized participants.

Statistical analyses

Statistical analysis title	Time to Progression (TTP)

Statistical analysis description:

HR with 95% CI was estimated using a stratified Cox proportional hazards regression model using the IWRS stratification factors.

Comparison groups	Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	1144
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.033 [12]
Method	Stratified Log Rank (SLR)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	0.99

Notes:

[11] - Superiority or Other (legacy)

[12] - SLR used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions.

Secondary: Percentage of Participants with Complete Response (CR) or Partial Response (PR) (Objective Response Rate)

End point title	Percentage of Participants with Complete Response (CR) or Partial Response (PR) (Objective Response Rate)

End point description:

Objective response rate (ORR) was defined as the percentage of randomized participants achieving a best confirmed overall response of CR or PR using Response Evaluation Criteria in Solid Tumors (RECIST v1.0), based on the achievement of both measurement and confirmation criteria; by Investigator assessment. CR was defined as the disappearance of all target and non-target lesions. PR was defined as at least a 30% decrease in the sum of the longest diameters (LD) of target lesions, taking as reference the baseline sum LD and no progression in non-target lesions.

End point type	Secondary

End point timeframe:

Randomization to disease progression or until data cutoff of 31-Mar-2013 (up to 56 months)

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	759[13]	385[14]		
Units: percentage of participants				
number (confidence interval 95%)	44.7 (41.1 to 48.3)	37.9 (33.1 to 43.0)		

Notes:

[13] - Intent-to-Treat (ITT) Population: All randomized participants.

[14] - Intent-to-Treat (ITT) Population: All randomized participants.

Statistical analyses

Statistical analysis title	Objective Response Rate

Statistical analysis description:

Stratified odds ratio was calculated considering the IWRS stratification factors.

Comparison groups	Placebo + Docetaxel v Ramucirumab (IMC-1121B) + Docetaxel

Number of subjects included in analysis	1144
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.027 [16]
Method	Stratified Cochran-Mantel-Haenszel(SCMH)
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.71

Notes:

[15] - Superiority or Other (legacy)

[16] - SCMH used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions.

Secondary: Duration of Response

End point title	Duration of Response

End point description:

Duration of complete response (CR) or partial response (PR) measured from time criteria were first met for CR or PR until first date of progressive disease (PD) or death from any cause defined using RECIST 1.0; by Investigator assessment.CR defined as disappearance of all target and non-target lesions.PR defined as ≥30% decrease in sum of LD of target lesions and no progression in non-target lesions.PD defined as ≥20% increase in LD sum of target lesions taking as reference the smallest sum LD since baseline,progression in non-target lesions or the appearance of ≥1 new lesion(s).Participants who did not relapse or die censored at day of last radiographic tumor assessment.If death or PD was after ≥2 missing radiographic visits, censoring was at date of last radiographic visit prior to missed visits. Symptomatic/clinical disease progression without documented radiologic progression did not constitute progression. Censored participants: ramucirumab + docetaxel=80, placebo + docetaxel=28.

End point type	Secondary

End point timeframe:

Date of first CR or PR to PD or death or until data cutoff date of 31-Mar-2013 (up to 56 months)

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	339[17]	146[18]		
Units: months				
median (confidence interval 95%)	8.4 (8.0 to 9.7)	8.1 (6.8 to 8.9)		

Notes:

[17] - A subset of the Intent-to-Treat (ITT) Population: all randomized participants with CR or PR.

[18] - A subset of the Intent-to-Treat (ITT) Population: all randomized participants with CR or PR.

Statistical analyses

Statistical analysis title	Duration of Response

Statistical analysis description:

HR with 95% CI was estimated using a stratified Cox proportional hazards regression model using the IWRS stratification factors.

Comparison groups	Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.15 [20]
Method	Stratified Log Rank (SLR)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.06

Notes:

[19] - Superiority or Other (legacy)

[20] - SLR used Interactive Web Response System (IWRS) factors: prior taxane therapy, visceral metastasis, hormone receptor status and geographical regions.

Secondary: Total Functional Assessment of Cancer Therapy-Breast (FACT-B): Change From Baseline to End of Therapy

End point title	Total Functional Assessment of Cancer Therapy-Breast (FACT-B): Change From Baseline to End of Therapy

End point description:

FACT-B measures the following domains of health-related quality of life (HR-QoL): physical well-being (PWB), social/family well-being (SFWB), emotional well-being (EWB), functional well-being (FWB), and additional concerns of breast cancer subscale (BCS) each with 6 or more items developed to measure problems specific to breast cancer symptoms plus additional items related to global QoL. Participants (pts) respond to each of the 36 questions on a 5-point scale from 0 (not at all) to 4 (very much) with a total scores range of 0-144. Higher scores indicate fewer symptoms and better HR-QoL.

End point type	Secondary

End point timeframe:

Baseline, End of Therapy or until data cutoff of 31-Mar-2013 (up to 56 months)

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	494[21]	251[22]		
Units: units on a scale				
arithmetic mean (standard deviation)	-6.8 (± 17.3)	-7.0 (± 16.8)		

Notes:

[21] - A subset of ITT Population: all randomized pts with a valid baseline and end of therapy assesments.

[22] - A subset of ITT Population: all randomized pts with a valid baseline and end of therapy assesments.

Statistical analyses

Statistical analysis title	FACT-B: Change From Baseline to End of Therapy
Comparison groups	Ramucirumab (IMC-1121B) + Docetaxel v Placebo + Docetaxel

Number of subjects included in analysis	745
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.539 [24]
Method	ANCOVA

Notes:

[23] - Superiority or Other (legacy)

[24] - P-value is for end of therapy. Analysis of covariance (ANCOVA) adjusted for baseline score was used to compare the 2 treatment arms.

Secondary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events

End point description:

Clinically significant events were defined as serious adverse events (SAE) and other treatment-emergent non-serious adverse events (NSAE). A summary of SAEs and other NSAEs is located in the Reported Adverse Event module.

End point type	Secondary

End point timeframe:

First dose to study completion (up to 12.3 years)

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	752[25]	382[26]		
Units: participants				
number (not applicable)				
Participants with SAEs	286	117		
Participants with NSAEs	738	373		

Notes:

[25] - All randomized participants who received at least 1 dose of study drug.

[26] - All randomized participants who received at least 1 dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Percentage of Participants With Treatment Emergent Anti-Ramucirumab Antibodies Until Primary Data Cutoff of 31-Mar-2013

End point title	Immunogenicity: Percentage of Participants With Treatment Emergent Anti-Ramucirumab Antibodies Until Primary Data Cutoff of 31-Mar-2013

End point description:

Percentage of participants with treatment-emergent positive for anti-ramucirumab (IMC-1121B) antibodies during the study. Participants were considered positive for anti-ramucirumab (IMC-1121B) antibodies if they exhibited a post-treatment antibody level that exceeded the positive upper cut point determined from the anti-ramucirumab (IMC-1121B) level seen in healthy untreated individuals. Analysis population included all randomized participants who received at least 1 dose of study drug with anti-IMC-1121B antibodies samples collected during the study.

End point type	Secondary

End point timeframe:

Baseline, prior to cycle 3 infusion, prior to cycle 5 infusion, onset of infusion reaction, resolution of reaction and 30 days following the event up to 56 months

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	715	360		
Units: percentage of participants				
number (not applicable)	0.8	0.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Percentage of Participants Available After 31-Mar-2013 With Treatment Emergent Anti-Ramucirumab Antibodies Until Data Cutoff From 01-Apr-2013 to 08-Sep-2016

End point title	Immunogenicity: Percentage of Participants Available After 31-Mar-2013 With Treatment Emergent Anti-Ramucirumab Antibodies Until Data Cutoff From 01-Apr-2013 to 08-Sep-2016

End point description:

Percentage of participants with treatment-emergent positive for anti-ramucirumab (IMC-1121B) antibodies during the study. Participants were considered positive for anti-ramucirumab (IMC-1121B) antibodies if they exhibited a post-treatment antibody level that exceeded the positive upper cut point determined from the anti-ramucirumab (IMC-1121B) level seen in healthy untreated individuals. Analysis population included all follow-up participants (additional participants who were available after primary data cut off 31-Mar-13) who received at least 1 dose of study drug with anti-IMC-1121B antibodies samples collected during the study.

End point type	Secondary

End point timeframe:

Follow-up from 01-Apr-2013 to 08-Sep-2016 (Up to 56 -97 months)

End point values	Ramucirumab (IMC-1121B) + Docetaxel	Placebo + Docetaxel		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	22		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose to study completion (up to 12.3 years)

Adverse event reporting additional description:

All randomized participants who received at least 1 dose of study drug.Disease progression without clinical manifestation or death related to progressive disease (PD) was not to be reported as an AE. However, all deaths within 30 days of last dose reported as SAE, regardless of causality. PD itself reported as an SAE,if any of the SAE criteria met.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Placebo + Docetaxel

Reporting group description:

Placebo comparator for ramucirumab (IMC-1121B) administered at a dose of 10 mg/kg as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

Reporting group title	Ramucirumab (IMC-1121B) + Docetaxel

Reporting group description:

Ramucirumab (IMC-1121B) is administered at a dose of 10 milligrams per kilogram (mg/kg) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle. Docetaxel is administered at a dose of 75 milligrams per square meter (mg/m²) as a 1-hour intravenous infusion on Day 1 of each 21-day cycle.

Serious adverse events	Placebo + Docetaxel	Ramucirumab (IMC-1121B) + Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	117 / 382 (30.63%)	285 / 752 (37.90%)	
number of deaths (all causes)	9	30	
number of deaths resulting from adverse events	1	9	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
acute myeloid leukaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
breast cancer			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

colon cancer				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
haemangioma				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	2 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
malignant ascites				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
malignant neoplasm progression				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
malignant pleural effusion				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
metastases to central nervous system				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	1 / 382 (0.26%)	3 / 752 (0.40%)		
occurrences causally related to treatment / all	0 / 1	0 / 3		
deaths causally related to treatment / all	0 / 0	0 / 2		
metastases to meninges				
alternative dictionary used: MedDRA 18.0				

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neoplasm progression			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	
tumour embolism			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
deep vein thrombosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 382 (0.79%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	3 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
embolism			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (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 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypertensive crisis			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypotension			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 382 (0.52%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	2 / 2	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
jugular vein thrombosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lymphoedema			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
subclavian vein thrombosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
therapy change			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	5 / 752 (0.66%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
chills			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
complication associated with device			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 382 (0.52%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
death			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	2 / 2	
disease progression			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	4 / 382 (1.05%)	8 / 752 (1.06%)	
occurrences causally related to treatment / all	0 / 4	1 / 8	
deaths causally related to treatment / all	0 / 4	0 / 6	
extravasation			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
face oedema			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
fatigue			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	10 / 752 (1.33%)	
occurrences causally related to treatment / all	1 / 1	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
general physical health deterioration			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
generalised oedema			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
inflammation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infusion site thrombosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
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 18.0				
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
mucosal inflammation				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
multiple organ dysfunction syndrome				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
oedema				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
oedema peripheral				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)		
occurrences causally related to treatment / all	0 / 0	2 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
pyrexia				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	2 / 382 (0.52%)	8 / 752 (1.06%)		
occurrences causally related to treatment / all	1 / 2	6 / 9		
deaths causally related to treatment / all	0 / 0	0 / 0		
sudden death				
alternative dictionary used: MedDRA 18.0				

subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 382 (0.79%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	3 / 3	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
disability			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
menstruation irregular			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
uterine haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
uterine polyp			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vaginal haemorrhage			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
acute interstitial pneumonitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	5 / 382 (1.31%)	5 / 752 (0.66%)	
occurrences causally related to treatment / all	2 / 6	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
epistaxis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemoptysis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
interstitial lung disease			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lung infiltration			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pleural effusion			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	6 / 382 (1.57%)	8 / 752 (1.06%)	
occurrences causally related to treatment / all	2 / 7	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumothorax			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
pulmonary embolism			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	4 / 382 (1.05%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	3 / 4	2 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
respiratory failure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
confusional state			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
depression			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mood altered			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 382 (0.52%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
thrombosis in device			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
blood calcium decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutrophil count decreased			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
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			
ankle fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
chemical burn of skin			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
expired product administered			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
facial bones fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
femur fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hip fracture			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
humerus fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ilium fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
incorrect dose administered			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
infusion related reaction			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
injury			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
medication error			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 382 (0.52%)	9 / 752 (1.20%)	
occurrences causally related to treatment / all	1 / 2	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

overdose				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	5 / 382 (1.31%)	7 / 752 (0.93%)		
occurrences causally related to treatment / all	1 / 11	4 / 13		
deaths causally related to treatment / all	0 / 0	0 / 0		
procedural pneumothorax				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
product administration error				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
product dispensing error				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	1 / 382 (0.26%)	3 / 752 (0.40%)		
occurrences causally related to treatment / all	2 / 2	1 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
product preparation issue				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
radiation oesophagitis				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
spinal fracture				
alternative dictionary used: MedDRA 18.0				

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
stoma site haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
suture rupture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
underdose			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	12 / 382 (3.14%)	11 / 752 (1.46%)	
occurrences causally related to treatment / all	0 / 24	4 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound dehiscence			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
wrong product administered			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
atrial fibrillation			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial flutter			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac failure congestive			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
left ventricular dysfunction			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericarditis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pericarditis constrictive			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

right ventricular failure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
supraventricular tachycardia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tachycardia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 382 (0.52%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
cerebral haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral ischaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebrovascular accident			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
demyelinating polyneuropathy			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
encephalopathy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
epilepsy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhagic stroke			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
headache			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	7 / 752 (0.93%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic encephalopathy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

hydrocephalus			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
loss of consciousness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
migraine			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nervous system disorder			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neuropathy peripheral			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
paraplegia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral motor neuropathy			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
radiculopathy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
seizure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
subarachnoid haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 382 (0.79%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	3 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
disseminated intravascular coagulation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
febrile neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	11 / 382 (2.88%)	51 / 752 (6.78%)	
occurrences causally related to treatment / all	12 / 12	57 / 57	
deaths causally related to treatment / all	0 / 0	1 / 1	
neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	20 / 382 (5.24%)	47 / 752 (6.25%)	
occurrences causally related to treatment / all	23 / 23	52 / 52	
deaths causally related to treatment / all	0 / 0	0 / 0	
thrombocytopenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

dacryostenosis acquired			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
panophthalmitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
papilloedema			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
visual acuity reduced			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (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 pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	1 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal fistula			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ascites			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
colitis ischaemic			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
constipation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 382 (0.52%)	9 / 752 (1.20%)	
occurrences causally related to treatment / all	2 / 2	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
diverticular perforation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
duodenitis haemorrhagic			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
enterocolitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

faecaloma			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastric ulcer perforation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastritis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhoids			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ileus paralytic			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal pseudo-obstruction			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
large intestinal ulcer			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
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 18.0			
subjects affected / exposed	0 / 382 (0.00%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
mouth haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	5 / 752 (0.66%)	
occurrences causally related to treatment / all	1 / 1	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
oesophagitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

rectal haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
retroperitoneal fibrosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
small intestinal haemorrhage			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
stomatitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	9 / 752 (1.20%)	
occurrences causally related to treatment / all	0 / 0	11 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 382 (0.52%)	7 / 752 (0.93%)	
occurrences causally related to treatment / all	2 / 2	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
cholecystitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholelithiasis			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic failure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
hepatic function abnormal			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
hepatic pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperbilirubinaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
liver disorder			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
dermatitis allergic			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
erythema nodosum			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lichen sclerosus			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
palmar-plantar erythrodysaesthesia syndrome			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rash			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin ulcer			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
subcutaneous emphysema			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	5 / 752 (0.66%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	2 / 2	
dysuria			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
proteinuria			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal failure			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
renal impairment			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ureteric obstruction			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary retention			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
back pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
bone pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
muscular weakness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
musculoskeletal chest pain			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
musculoskeletal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
myalgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
myositis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteonecrosis of jaw			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pain in extremity			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pathological fracture			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

spinal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
abdominal infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominal wall abscess			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abscess intestinal			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abscess limb			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abscess soft tissue			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal abscess			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
catheter site infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
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 18.0			
subjects affected / exposed	0 / 382 (0.00%)	8 / 752 (1.06%)	
occurrences causally related to treatment / all	0 / 0	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
clostridium difficile colitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
clostridium difficile infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

device related infection				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)		
occurrences causally related to treatment / all	0 / 0	1 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
diverticulitis				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	1 / 1	2 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastroenteritis				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastroenteritis viral				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (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 18.0				
subjects affected / exposed	0 / 382 (0.00%)	4 / 752 (0.53%)		
occurrences causally related to treatment / all	0 / 0	2 / 4		
deaths causally related to treatment / all	0 / 0	0 / 0		
lower respiratory tract infection				
alternative dictionary used: MedDRA 18.0				
subjects affected / exposed	1 / 382 (0.26%)	3 / 752 (0.40%)		
occurrences causally related to treatment / all	0 / 1	1 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
lymphangitis				
alternative dictionary used: MedDRA 18.0				

subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
mastitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
mucosal infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutropenic infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	9 / 382 (2.36%)	19 / 752 (2.53%)	
occurrences causally related to treatment / all	10 / 10	18 / 19	
deaths causally related to treatment / all	0 / 0	1 / 1	
neutropenic sepsis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	7 / 752 (0.93%)	
occurrences causally related to treatment / all	0 / 0	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
oral herpes			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteomyelitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

pelvic abscess			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peritonitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	5 / 382 (1.31%)	15 / 752 (1.99%)	
occurrences causally related to treatment / all	3 / 5	8 / 16	
deaths causally related to treatment / all	0 / 0	0 / 1	
pneumonia chlamydial			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative wound infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal abscess			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratory tract infection			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
retroperitoneal abscess			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	7 / 752 (0.93%)	
occurrences causally related to treatment / all	0 / 0	4 / 7	
deaths causally related to treatment / all	0 / 0	1 / 2	
sinusitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
skin infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
staphylococcal sepsis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
streptococcal infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

tonsillitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
tooth abscess			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	1 / 1	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
urinary tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	3 / 382 (0.79%)	6 / 752 (0.80%)	
occurrences causally related to treatment / all	3 / 3	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
vascular device infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	1 / 1	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
viral upper respiratory tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
wound infection			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
dehydration			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	7 / 752 (0.93%)	
occurrences causally related to treatment / all	0 / 0	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
diabetes mellitus inadequate control			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fluid overload			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	0 / 752 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fluid retention			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypercalcaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	1 / 382 (0.26%)	4 / 752 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoglycaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	2 / 752 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	3 / 752 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyponatraemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lactic acidosis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	0 / 382 (0.00%)	1 / 752 (0.13%)	
occurrences causally related to treatment / all	0 / 0	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 + Docetaxel	Ramucirumab (IMC-1121B) + Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	373 / 382 (97.64%)	737 / 752 (98.01%)	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	44 / 382 (11.52%)	204 / 752 (27.13%)	
occurrences (all)	96	405	
hot flush			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	21 / 382 (5.50%)	34 / 752 (4.52%)	
occurrences (all)	22	44	
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	127 / 382 (33.25%)	270 / 752 (35.90%)	
occurrences (all)	363	549	
face oedema			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	27 / 382 (7.07%)	73 / 752 (9.71%)	
occurrences (all)	30	100	
fatigue			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	135 / 382 (35.34%)	271 / 752 (36.04%)	
occurrences (all)	240	481	
influenza like illness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	29 / 382 (7.59%)	39 / 752 (5.19%)	
occurrences (all)	40	48	
non-cardiac chest pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	19 / 382 (4.97%)	39 / 752 (5.19%)	
occurrences (all)	21	43	
oedema			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	18 / 382 (4.71%)	43 / 752 (5.72%)	
occurrences (all)	26	48	
oedema peripheral			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	101 / 382 (26.44%)	181 / 752 (24.07%)	
occurrences (all)	140	274	
pyrexia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	44 / 382 (11.52%)	110 / 752 (14.63%)	
occurrences (all)	65	168	
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	69 / 382 (18.06%)	127 / 752 (16.89%)	
occurrences (all)	89	179	
dyspnoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	75 / 382 (19.63%)	163 / 752 (21.68%)	
occurrences (all)	90	225	
epistaxis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	64 / 382 (16.75%)	300 / 752 (39.89%)	
occurrences (all)	149	817	
oropharyngeal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	27 / 382 (7.07%)	65 / 752 (8.64%)	
occurrences (all)	36	96	
pleural effusion			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	28 / 382 (7.33%)	69 / 752 (9.18%)	
occurrences (all)	29	74	
rhinorrhoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	19 / 382 (4.97%)	56 / 752 (7.45%)	
occurrences (all)	23	82	
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	27 / 382 (7.07%)	49 / 752 (6.52%)	
occurrences (all)	27	65	
insomnia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	33 / 382 (8.64%)	99 / 752 (13.16%)	
occurrences (all)	39	127	
Investigations			
weight increased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	92 / 382 (24.08%)	123 / 752 (16.36%)	
occurrences (all)	105	152	
weight decreased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	41 / 382 (10.73%)	173 / 752 (23.01%)	
occurrences (all)	50	209	
Injury, poisoning and procedural complications			
infusion related reaction			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	24 / 382 (6.28%)	41 / 752 (5.45%)	
occurrences (all)	43	56	
Cardiac disorders			
tachycardia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	23 / 382 (6.02%)	50 / 752 (6.65%)	
occurrences (all)	36	70	
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	36 / 382 (9.42%)	64 / 752 (8.51%)	
occurrences (all)	45	88	
dysgeusia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	32 / 382 (8.38%)	68 / 752 (9.04%)	
occurrences (all)	66	120	
headache			

alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	70 / 382 (18.32%)	171 / 752 (22.74%)	
occurrences (all)	98	306	
neuropathy peripheral			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	64 / 382 (16.75%)	101 / 752 (13.43%)	
occurrences (all)	78	124	
paraesthesia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	31 / 382 (8.12%)	47 / 752 (6.25%)	
occurrences (all)	40	59	
peripheral sensory neuropathy			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	73 / 382 (19.11%)	136 / 752 (18.09%)	
occurrences (all)	90	193	
taste disorder			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	58 / 382 (15.18%)	105 / 752 (13.96%)	
occurrences (all)	89	156	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	28 / 382 (7.33%)	77 / 752 (10.24%)	
occurrences (all)	39	108	
neutropenia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	41 / 382 (10.73%)	96 / 752 (12.77%)	
occurrences (all)	56	175	
Eye disorders			
lacrimation increased			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	65 / 382 (17.02%)	233 / 752 (30.98%)	
occurrences (all)	90	337	
Gastrointestinal disorders			

abdominal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	42 / 382 (10.99%)	95 / 752 (12.63%)	
occurrences (all)	59	141	
abdominal pain upper			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	24 / 382 (6.28%)	51 / 752 (6.78%)	
occurrences (all)	33	71	
constipation			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	74 / 382 (19.37%)	157 / 752 (20.88%)	
occurrences (all)	116	293	
diarrhoea			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	152 / 382 (39.79%)	326 / 752 (43.35%)	
occurrences (all)	338	751	
dry mouth			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	20 / 382 (5.24%)	29 / 752 (3.86%)	
occurrences (all)	33	54	
dyspepsia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	40 / 382 (10.47%)	75 / 752 (9.97%)	
occurrences (all)	57	110	
gingival bleeding			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	2 / 382 (0.52%)	73 / 752 (9.71%)	
occurrences (all)	2	144	
haemorrhoids			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	8 / 382 (2.09%)	39 / 752 (5.19%)	
occurrences (all)	8	50	
nausea			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	156 / 382 (40.84%)	278 / 752 (36.97%)	
occurrences (all)	343	766	
stomatitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	118 / 382 (30.89%)	380 / 752 (50.53%)	
occurrences (all)	215	833	
vomiting			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	80 / 382 (20.94%)	155 / 752 (20.61%)	
occurrences (all)	127	288	
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	279 / 382 (73.04%)	535 / 752 (71.14%)	
occurrences (all)	287	550	
dry skin			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	21 / 382 (5.50%)	55 / 752 (7.31%)	
occurrences (all)	21	60	
nail disorder			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	105 / 382 (27.49%)	231 / 752 (30.72%)	
occurrences (all)	114	250	
palmar-plantar erythrodysaesthesia syndrome			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	33 / 382 (8.64%)	106 / 752 (14.10%)	
occurrences (all)	36	157	
pruritus			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	21 / 382 (5.50%)	41 / 752 (5.45%)	
occurrences (all)	23	44	
rash			
alternative dictionary used: MedDRA 18.0			

subjects affected / exposed	47 / 382 (12.30%)	109 / 752 (14.49%)	
occurrences (all)	63	143	
Renal and urinary disorders			
proteinuria			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	5 / 382 (1.31%)	44 / 752 (5.85%)	
occurrences (all)	5	75	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	82 / 382 (21.47%)	173 / 752 (23.01%)	
occurrences (all)	167	359	
back pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	54 / 382 (14.14%)	114 / 752 (15.16%)	
occurrences (all)	74	143	
bone pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	41 / 382 (10.73%)	92 / 752 (12.23%)	
occurrences (all)	82	192	
musculoskeletal pain			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	18 / 382 (4.71%)	51 / 752 (6.78%)	
occurrences (all)	32	105	
myalgia			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	89 / 382 (23.30%)	153 / 752 (20.35%)	
occurrences (all)	209	292	
pain in extremity			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	47 / 382 (12.30%)	107 / 752 (14.23%)	
occurrences (all)	66	195	
Infections and infestations			

conjunctivitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	17 / 382 (4.45%)	38 / 752 (5.05%)	
occurrences (all)	25	42	
nasopharyngitis			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	20 / 382 (5.24%)	63 / 752 (8.38%)	
occurrences (all)	30	79	
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	21 / 382 (5.50%)	39 / 752 (5.19%)	
occurrences (all)	29	48	
urinary tract infection			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	28 / 382 (7.33%)	71 / 752 (9.44%)	
occurrences (all)	32	91	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.0			
subjects affected / exposed	62 / 382 (16.23%)	165 / 752 (21.94%)	
occurrences (all)	101	293	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2008	Important overall changes included additional instructions related infusion and shelf life of Ramucirumab, and instructions to report any Grade 3 or 4 AE as an 'important medical event' using the serious adverse event report (SAER) form.
23 April 2009	Important overall changes included new details on prohibited therapies, expanded to include hormonal therapy; additional instructions related to the preparation and administration of study drugs, and SAEs reporting.
06 December 2010	Important overall changes included the addition of an inclusion criterion to specify that participants that received prior biologic therapy in the metastatic setting were not eligible, changes to the interim analyses plan, with a reduction to one single analysis at 40% of the expected PFS events; updates to the unblinding procedures and reporting SAEs and other updates in different sections of the protocol, including pre-medications.
23 April 2012	Important overall changes included updates on the assessment of PFS and response-related endpoints, clarifications and details related to the OS analysis, additional instructions for the management of the reversible posterior leukoencephalopathy syndrome (RPLS) and other more administrative updates.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

One participant assigned to placebo + docetaxel (doc) treatment and was given ramucirumab (ram) in Cycle 1. Considered ram + doc treatment arm for safety population, for ITT population the participant was analyzed according to assigned treatment.

Notes: