Clinical trial results:
A 3-Arm Phase 2 Double-Blind Randomized Study of Gemcitabine, Abraxane® plus Placebo versus Gemcitabine, Abraxane® plus 1 or 2 Truncated Courses of Demcizumab in Subjects with 1st-Line Metastatic Pancreatic Ductal Adenocarcinoma

Summary

EudraCT number	2014-003355-56
Trial protocol	ES GB BE
Global end of trial date	08 May 2017

Results information

Result version number	v1 (current)
This version publication date	07 December 2017
First version publication date	07 December 2017

Trial information

Trial identification

Sponsor protocol code	M18-006

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	OncoMed Pharmaceuticals, Inc
Sponsor organisation address	800 Chesapeake Drive, Redwood City, CA, United States, 94063
Public contact	Robert Stagg, VP, Clinical Research, OncoMed Pharmaceuticals, Inc., +1 925 3239548, Robert.stagg@oncomed.com
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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 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 May 2017
Global end of trial reached?	Yes
Global end of trial date	08 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare the efficacy of placebo/placebo arm to the pooled demcizumab arm (i.e., placebo/placebo arm to demcizumab/placebo and demcizumab/demcizumab arms) in subjects with first-line metastatic pancreatic ductal adenocarcinoma.

Protection of trial subjects:

Subjects experiencing a Grade 2 infusion reaction of dyspnea (asymptomatic bronchospasm) or generalized urticaria should be premedicated prior to subsequent infusions.Premedications may include medications such as corticosteroids, diphenhydramine, and/or bronchodialators as indicated. If an infusion reaction occurred, administration was stopped and appropriate medical care was administered. Once the infusion reaction was resolved, and at investigator discretion, the infusion was resumed at one-half of the initial rate of infusion. All subsequent infusions for that subject were then administered at the reduced rate of infusion.

Background therapy:

Subjects who received adjuvant hormonal therapy, such as tamoxifen for a history of breast cancer, continued to receive this treatment. A deep venous thrombosis prophylaxis during a hospitalization according to institutional standards was permitted.

Evidence for comparator: -

Actual start date of recruitment	31 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 56
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Spain: 71
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Belgium: 6
Worldwide total number of subjects	204
EEA total number of subjects	86

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)	100
From 65 to 84 years	103
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Subjects aged ≥21 years with cytologically or histologically confirmed metastatic pancreatic ductal adenocarcinoma were included. Prior chemotherapy and/or radiotherapy either in the adjuvant or neoadjuvant setting or for metastatic disease was not allowed.

Pre-assignment

Screening details:

Prior to randomization, subjects underwent screening to determine study eligibility. Screening assessments were to include CT scans of the chest, abdomen, and pelvis, as well as MRI of the brain. CT scan of the neck or bone scan was performed if clinically indicated.

Period 1

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

Blinding implementation details:

This was a Phase 2, randomized, double-blind controlled study. Placebo was a clear to slightly opalescent, colorless to slightly yellow liquid formulation of 50 mM histidine, 100 mM sodium chloride, 45 mM sucrose, and 0.01% (v/v) polysorbate-20, pH 6.0.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo/placebo arm

Arm description:

Abraxane and gemcitabine plus placebo (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.

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

Dosage and administration details:

Placebo was a clear to slightly opalescent, colorless to slightly yellow liquid formulation of 50 mM histidine, 100 mM sodium chloride, 45 mM sucrose, and 0.01% (v/v) polysorbate-20, pH 6.0.

Arm title	Demcizumab/placebo

Arm description:

Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.

Arm type	Active comparator
Investigational medicinal product name	Demcizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Demcizumab 3.5 mg/kg (or placebo) was administered once every 2 weeks for 6 doses (i.e., the last dose was given on Day 70). A second course of demcizumab 3.5 mg/kg or placebo was administered once every 2 weeks for 6 doses starting at Day 168 if the subject's Day 168 BNP was ≤100 pg/mL, peak tricuspid velocity was ≤3.0 m/s, and LVEF was ≥50%, and the subject had not developed pulmonary

hypertension or heart failure while on study. No dose reductions were allowed for required modifications of demcizumab/placebo dosing.

Demcizumab was supplied at a concentration of 10 mg/mL in a 25-mL single-use glass vial filled to 20 mL to deliver a total of 200 mg per vial.

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

Dosage and administration details:

Placebo was a clear to slightly opalescent, colorless to slightly yellow liquid formulation of 50 mM histidine, 100 mM sodium chloride, 45 mM sucrose, and 0.01% (v/v) polysorbate-20, pH 6.0.

Arm title	Demcizumab/demcizumab

Arm description:

Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus demcizumab (3 cycles), and then Abraxane and gemcitabine until disease progression.

Arm type	Experimental
Investigational medicinal product name	Demcizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Demcizumab 3.5 mg/kg (or placebo) was administered once every 2 weeks for 6 doses (i.e., the last dose was given on Day 70). A second course of demcizumab 3.5 mg/kg or placebo was administered once every 2 weeks for 6 doses starting at Day 168 if the subject's Day 168 BNP was ≤100 pg/mL, peak tricuspid velocity was ≤3.0 m/s, and LVEF was ≥50%, and the subject had not developed pulmonary hypertension or heart failure while on study. No dose reductions were allowed for required modifications of demcizumab/placebo dosing.

Demcizumab was supplied at a concentration of 10 mg/mL in a 25-mL single-use glass vial filled to 20 mL to deliver a total of 200 mg per vial.

Number of subjects in period 1	Placebo/placebo arm	Demcizumab/placebo	Demcizumab/demcizumab
Started	68	71	65
Completed	16	18	9
Not completed	52	53	56
Use of other anticancer therapy	-	-	1
Physician decision	2	5	2
Consent withdrawn by subject	-	4	1
Disease progression	34	28	34
Adverse event, non-fatal	3	5	5
Death	5	4	3
Other	8	7	10

Baseline characteristics

Reporting groups	
Reporting group title	Placebo/placebo arm
Reporting group description:	
Abraxane and gemcitabine plus placebo (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.	
Reporting group title	Demcizumab/placebo
Reporting group description:	
Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.	
Reporting group title	Demcizumab/demcizumab
Reporting group description:	
Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus demcizumab (3 cycles), and then Abraxane and gemcitabine until disease progression.	

Reporting group values	Placebo/placebo arm	Demcizumab/placebo	Demcizumab/demcizumab
Number of subjects	68	71	65
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	37	34	30
From 65-84 years	31	36	35
85 years and over	0	1	0
Gender categorical Units: Subjects			
Female	27	31	30
Male	41	40	35

Reporting group values	Total		
Number of subjects	204		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	101		
From 65-84 years	102		

85 years and over	1		

Gender categorical Units: Subjects			
Female	88		
Male	116		

Subject analysis sets

Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population comprised all subjects who received at least 1 partial or complete dose of demcizumab or placebo. All baseline characteristics and demographic, efficacy, immunogenicity, and biomarker data were analyzed using the ITT population.

Reporting group values	ITT analysis set		
Number of subjects	204		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Gender categorical Units: Subjects			
Female	88		
Male	116		

End points

End points reporting groups

Reporting group title	Placebo/placebo arm

Reporting group description:

Abraxane and gemcitabine plus placebo (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.

Reporting group title	Demcizumab/placebo

Reporting group description:

Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus placebo (3 cycles), and then Abraxane and gemcitabine until disease progression.

Reporting group title	Demcizumab/demcizumab

Reporting group description:

Abraxane and gemcitabine plus demcizumab (3 cycles), Abraxane and gemcitabine (3 cycles), Abraxane and gemcitabine plus demcizumab (3 cycles), and then Abraxane and gemcitabine until disease progression.

Subject analysis set title	ITT analysis set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population comprised all subjects who received at least 1 partial or complete dose of demcizumab or placebo. All baseline characteristics and demographic, efficacy, immunogenicity, and biomarker data were analyzed using the ITT population.

Primary: To compare the hazard of progression in the placebo/placebo arm and the pooled demcizumab arm

End point title	To compare the hazard of progression in the placebo/placebo arm and the pooled demcizumab arm

End point description:

The primary endpoint is to compare the hazard of progression using the investigator-assessed progression-free survival (PFS) time between subjects in the placebo/placebo arm and the pooled demcizumab arm (i.e., demcizumab/placebo arm + demcizumab/demcizumab arm) in first-line metastatic pancreatic ductal adenocarcinoma.

End point type	Primary

End point timeframe:

Investigator-assessed progression-free survival (PFS) time.

End point values	Placebo/placebo arm	Demcizumab/placebo	Demcizumab/demcizumab	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	68	71	65	
Units: progression-free survival (PFS) time				
number (not applicable)	68	71	65	

Statistical analyses

Statistical analysis title	Statistical analysis plan dated 08 March 2017

Statistical analysis description:

Efficacy was compared of placebo/placebo arm to the pooled demcizumab arm (i.e., placebo/placebo

arm to demcizumab/placebo and demcizumab/demcizumab arms) in subjects with first-line metastatic pancreatic ductal adenocarcinoma.

Comparison groups	Demcizumab/placebo v Demcizumab/demcizumab v Placebo/placebo arm
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.7158
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.81
upper limit	7.36
Variability estimate	Standard deviation

Notes:

[1] - Gemcitabine was administered by intravenous (IV) infusion at a dose of 1000 mg/m2 on Days 1, 8, and 15 of each 28-day treatment cycle. Abraxane was administered by IV infusion at a dose of 125 mg/m2 over 30 minutes on Days 1, 8, and 15 of each 28-day treatment cycle. Demcizumab 3.5 mg/kg or placebo was administered by IV infusion (prior to the administration of Abraxane and gemcitabine) once every 2 weeks for either 1 or 2 70-day courses.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Investigators were required to follow their respective IRB or IEC requirements for the reporting of serious adverse events (SAEs)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo/placebo
Reporting group description: -	
Reporting group title	Demcizumab/placebo
Reporting group description: -	
Reporting group title	Demcizumab/Demcizumab

Reporting group description: -

Serious adverse events	Placebo/placebo	Demcizumab/placebo	Demcizumab/Demcizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 68 (58.82%)	49 / 71 (69.01%)	34 / 65 (52.31%)
number of deaths (all causes)	5	12	3
number of deaths resulting from adverse events	5	12	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic neoplasm			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tumour rupture			

subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 68 (8.82%)	3 / 71 (4.23%)	6 / 65 (9.23%)
occurrences causally related to treatment / all	1 / 6	1 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 68 (2.94%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 68 (2.94%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	2 / 68 (2.94%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 68 (0.00%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Orthopnoea			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 68 (1.47%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Investigations			
Blood bilirubin increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 68 (2.94%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 68 (1.47%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaesthetic complication			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hip fracture			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 68 (0.00%)	2 / 71 (2.82%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 68 (0.00%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Syncope			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral infarction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peroneal nerve palsy			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Febrile neutropenia			
subjects affected / exposed	4 / 68 (5.88%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Anaemia			
subjects affected / exposed	3 / 68 (4.41%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 68 (1.47%)	1 / 71 (1.41%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic anaemia			
subjects affected / exposed	0 / 68 (0.00%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloedema			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	5 / 68 (7.35%)	4 / 71 (5.63%)	5 / 65 (7.69%)
occurrences causally related to treatment / all	1 / 5	1 / 4	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 68 (1.47%)	4 / 71 (5.63%)	3 / 65 (4.62%)
occurrences causally related to treatment / all	1 / 1	1 / 4	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	4 / 68 (5.88%)	0 / 71 (0.00%)	3 / 65 (4.62%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	4 / 68 (5.88%)	1 / 71 (1.41%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 4	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	2 / 71 (2.82%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Ascites			

subjects affected / exposed	1 / 68 (1.47%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 68 (1.47%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 68 (0.00%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Small intestinal haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anal fissure			

subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic fistula			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal stenosis			

subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic duct obstruction			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic insufficiency			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Jaundice cholestatic			
subjects affected / exposed	1 / 68 (1.47%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	1 / 68 (1.47%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct obstruction			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bile duct stenosis			

subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haematoma			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Portal vein thrombosis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			

subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	3 / 65 (4.62%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal injury			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 68 (2.94%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral lesion			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Sepsis			
subjects affected / exposed	3 / 68 (4.41%)	4 / 71 (5.63%)	4 / 65 (6.15%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Liver abscess			
subjects affected / exposed	2 / 68 (2.94%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 68 (2.94%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 68 (1.47%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 68 (2.94%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Urosepsis			
subjects affected / exposed	2 / 68 (2.94%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 68 (0.00%)	2 / 71 (2.82%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			

subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic infection			

subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tick-borne fever			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 68 (0.00%)	1 / 71 (1.41%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 68 (2.94%)	3 / 71 (4.23%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 2	1 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	2 / 65 (3.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Food intolerance			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 68 (1.47%)	0 / 71 (0.00%)	0 / 65 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 68 (0.00%)	0 / 71 (0.00%)	1 / 65 (1.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo/placebo	Demcizumab/placebo	Demcizumab/Demcizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	68 / 68 (100.00%)	71 / 71 (100.00%)	65 / 65 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 68 (14.71%)	17 / 71 (23.94%)	21 / 65 (32.31%)
occurrences (all)	10	17	21
Hypotension			
subjects affected / exposed	11 / 68 (16.18%)	6 / 71 (8.45%)	5 / 65 (7.69%)
occurrences (all)	11	6	5
Deep vein thrombosis			
subjects affected / exposed	7 / 68 (10.29%)	4 / 71 (5.63%)	9 / 65 (13.85%)
occurrences (all)	7	4	9
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	34 / 68 (50.00%)	31 / 71 (43.66%)	37 / 65 (56.92%)
occurrences (all)	34	31	37
Oedema peripheral			
subjects affected / exposed	29 / 68 (42.65%)	39 / 71 (54.93%)	34 / 65 (52.31%)
occurrences (all)	29	39	34
Pyrexia			
subjects affected / exposed	24 / 68 (35.29%)	30 / 71 (42.25%)	23 / 65 (35.38%)
occurrences (all)	24	30	23
Asthenia			
subjects affected / exposed	18 / 68 (26.47%)	27 / 71 (38.03%)	20 / 65 (30.77%)
occurrences (all)	18	27	20
Chills			
subjects affected / exposed	6 / 68 (8.82%)	3 / 71 (4.23%)	8 / 65 (12.31%)
occurrences (all)	6	3	8
Headache			
subjects affected / exposed	12 / 68 (17.65%)	13 / 71 (18.31%)	22 / 65 (33.85%)
occurrences (all)	12	13	22
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	18 / 68 (26.47%)	16 / 71 (22.54%)	10 / 65 (15.38%)
occurrences (all)	18	16	10
Epistaxis			
subjects affected / exposed	10 / 68 (14.71%)	13 / 71 (18.31%)	17 / 65 (26.15%)
occurrences (all)	10	13	17
Cough			
subjects affected / exposed	10 / 68 (14.71%)	12 / 71 (16.90%)	11 / 65 (16.92%)
occurrences (all)	10	12	11
Dyspnoea exertional			
subjects affected / exposed	3 / 68 (4.41%)	4 / 71 (5.63%)	8 / 65 (12.31%)
occurrences (all)	3	4	8
Pulmonary hypertension			
subjects affected / exposed	1 / 68 (1.47%)	7 / 71 (9.86%)	7 / 65 (10.77%)
occurrences (all)	1	7	7
Rhinorrhoea			

subjects affected / exposed	5 / 68 (7.35%)	2 / 71 (2.82%)	5 / 65 (7.69%)
occurrences (all)	5	2	5
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 68 (13.24%)	8 / 71 (11.27%)	9 / 65 (13.85%)
occurrences (all)	9	8	9
Anxiety			
subjects affected / exposed	10 / 68 (14.71%)	5 / 71 (7.04%)	3 / 65 (4.62%)
occurrences (all)	10	5	3
Depression			
subjects affected / exposed	6 / 68 (8.82%)	3 / 71 (4.23%)	7 / 65 (10.77%)
occurrences (all)	6	3	7
Investigations			
Platelet count decreased			
subjects affected / exposed	16 / 68 (23.53%)	20 / 71 (28.17%)	13 / 65 (20.00%)
occurrences (all)	16	20	13
Alanine aminotransferase increased			
subjects affected / exposed	16 / 68 (23.53%)	15 / 71 (21.13%)	15 / 65 (23.08%)
occurrences (all)	16	15	15
Neutrophil count decreased			
subjects affected / exposed	16 / 68 (23.53%)	12 / 71 (16.90%)	12 / 65 (18.46%)
occurrences (all)	16	12	12
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 68 (19.12%)	5 / 71 (7.04%)	12 / 65 (18.46%)
occurrences (all)	13	5	12
Brain natriuretic peptide increased			
subjects affected / exposed	5 / 68 (7.35%)	11 / 71 (15.49%)	14 / 65 (21.54%)
occurrences (all)	5	11	14
White blood cell count decreased			
subjects affected / exposed	9 / 68 (13.24%)	4 / 71 (5.63%)	10 / 65 (15.38%)
occurrences (all)	9	4	10
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 68 (7.35%)	6 / 71 (8.45%)	10 / 65 (15.38%)
occurrences (all)	5	6	10
Weight decreased			

subjects affected / exposed	8 / 68 (11.76%)	5 / 71 (7.04%)	8 / 65 (12.31%)
occurrences (all)	8	5	8
Blood bilirubin increased			
subjects affected / exposed	6 / 68 (8.82%)	3 / 71 (4.23%)	3 / 65 (4.62%)
occurrences (all)	6	3	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 68 (7.35%)	2 / 71 (2.82%)	5 / 65 (7.69%)
occurrences (all)	5	2	5
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	18 / 68 (26.47%)	16 / 71 (22.54%)	17 / 65 (26.15%)
occurrences (all)	18	16	17
Peripheral sensory neuropathy			
subjects affected / exposed	16 / 68 (23.53%)	17 / 71 (23.94%)	17 / 65 (26.15%)
occurrences (all)	16	17	17
Neuropathy peripheral			
subjects affected / exposed	11 / 68 (16.18%)	15 / 71 (21.13%)	12 / 65 (18.46%)
occurrences (all)	11	15	12
Dizziness			
subjects affected / exposed	10 / 68 (14.71%)	5 / 71 (7.04%)	7 / 65 (10.77%)
occurrences (all)	10	5	7
Neurotoxicity			
subjects affected / exposed	2 / 68 (2.94%)	11 / 71 (15.49%)	4 / 65 (6.15%)
occurrences (all)	2	11	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	27 / 68 (39.71%)	43 / 71 (60.56%)	35 / 65 (53.85%)
occurrences (all)	27	43	35
Thrombocytopenia			
subjects affected / exposed	15 / 68 (22.06%)	14 / 71 (19.72%)	16 / 65 (24.62%)
occurrences (all)	15	14	16
Neutropenia			
subjects affected / exposed	21 / 68 (30.88%)	24 / 71 (33.80%)	25 / 65 (38.46%)
occurrences (all)	21	24	25
Eye disorders			

Vision blurred			
subjects affected / exposed	3 / 68 (4.41%)	3 / 71 (4.23%)	5 / 65 (7.69%)
occurrences (all)	3	3	5
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	42 / 68 (61.76%)	38 / 71 (53.52%)	41 / 65 (63.08%)
occurrences (all)	42	38	41
Diarrhoea			
subjects affected / exposed	34 / 68 (50.00%)	41 / 71 (57.75%)	45 / 65 (69.23%)
occurrences (all)	34	41	45
Vomiting			
subjects affected / exposed	27 / 68 (39.71%)	32 / 71 (45.07%)	25 / 65 (38.46%)
occurrences (all)	27	32	25
Constipation			
subjects affected / exposed	20 / 68 (29.41%)	21 / 71 (29.58%)	28 / 65 (43.08%)
occurrences (all)	20	21	28
Abdominal pain			
subjects affected / exposed	24 / 68 (35.29%)	16 / 71 (22.54%)	27 / 65 (41.54%)
occurrences (all)	24	16	27
Stomatitis			
subjects affected / exposed	13 / 68 (19.12%)	12 / 71 (16.90%)	15 / 65 (23.08%)
occurrences (all)	13	12	15
Abdominal pain upper			
subjects affected / exposed	13 / 68 (19.12%)	6 / 71 (8.45%)	8 / 65 (12.31%)
occurrences (all)	13	6	8
Dry mouth			
subjects affected / exposed	7 / 68 (10.29%)	9 / 71 (12.68%)	6 / 65 (9.23%)
occurrences (all)	7	9	6
Ascites			
subjects affected / exposed	9 / 68 (13.24%)	6 / 71 (8.45%)	3 / 65 (4.62%)
occurrences (all)	9	6	3
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 68 (8.82%)	7 / 71 (9.86%)	5 / 65 (7.69%)
occurrences (all)	6	7	5
Abdominal distension			

subjects affected / exposed	5 / 68 (7.35%)	4 / 71 (5.63%)	4 / 65 (6.15%)
occurrences (all)	5	4	4
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	30 / 68 (44.12%)	33 / 71 (46.48%)	28 / 65 (43.08%)
occurrences (all)	30	33	28
Rash			
subjects affected / exposed	18 / 68 (26.47%)	14 / 71 (19.72%)	17 / 65 (26.15%)
occurrences (all)	18	14	17
Dry skin			
subjects affected / exposed	4 / 68 (5.88%)	5 / 71 (7.04%)	5 / 65 (7.69%)
occurrences (all)	4	5	5
Rash maculo-papular			
subjects affected / exposed	6 / 68 (8.82%)	3 / 71 (4.23%)	5 / 65 (7.69%)
occurrences (all)	6	3	5
Erythema			
subjects affected / exposed	3 / 68 (4.41%)	7 / 71 (9.86%)	3 / 65 (4.62%)
occurrences (all)	3	7	3
Hypokalaemia			
subjects affected / exposed	7 / 68 (10.29%)	7 / 71 (9.86%)	6 / 65 (9.23%)
occurrences (all)	7	7	6
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	16 / 68 (23.53%)	10 / 71 (14.08%)	13 / 65 (20.00%)
occurrences (all)	16	10	13
Myalgia			
subjects affected / exposed	6 / 68 (8.82%)	10 / 71 (14.08%)	15 / 65 (23.08%)
occurrences (all)	6	10	15
Arthralgia			
subjects affected / exposed	8 / 68 (11.76%)	9 / 71 (12.68%)	10 / 65 (15.38%)
occurrences (all)	8	9	10
Pain in extremity			
subjects affected / exposed	8 / 68 (11.76%)	5 / 71 (7.04%)	7 / 65 (10.77%)
occurrences (all)	8	5	7
Musculoskeletal pain			

subjects affected / exposed	3 / 68 (4.41%)	3 / 71 (4.23%)	6 / 65 (9.23%)
occurrences (all)	3	3	6
Muscular weakness			
subjects affected / exposed	5 / 68 (7.35%)	2 / 71 (2.82%)	4 / 65 (6.15%)
occurrences (all)	5	2	4
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	7 / 68 (10.29%)	5 / 71 (7.04%)	7 / 65 (10.77%)
occurrences (all)	7	5	7
Upper respiratory tract infection			
subjects affected / exposed	6 / 68 (8.82%)	6 / 71 (8.45%)	6 / 65 (9.23%)
occurrences (all)	6	6	6
Oral candidiasis			
subjects affected / exposed	8 / 68 (11.76%)	2 / 71 (2.82%)	4 / 65 (6.15%)
occurrences (all)	8	2	4
Cellulitis			
subjects affected / exposed	6 / 68 (8.82%)	5 / 71 (7.04%)	1 / 65 (1.54%)
occurrences (all)	6	5	1
Sepsis			
subjects affected / exposed	3 / 68 (4.41%)	5 / 71 (7.04%)	4 / 65 (6.15%)
occurrences (all)	3	5	4
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 68 (27.94%)	30 / 71 (42.25%)	27 / 65 (41.54%)
occurrences (all)	19	30	27
Hypoalbuminaemia			
subjects affected / exposed	8 / 68 (11.76%)	10 / 71 (14.08%)	9 / 65 (13.85%)
occurrences (all)	8	10	9
Dehydration			
subjects affected / exposed	6 / 68 (8.82%)	10 / 71 (14.08%)	6 / 65 (9.23%)
occurrences (all)	6	10	6
Hyperglycaemia			
subjects affected / exposed	11 / 68 (16.18%)	5 / 71 (7.04%)	4 / 65 (6.15%)
occurrences (all)	11	5	4
Hyponatraemia			

subjects affected / exposed	6 / 68 (8.82%)	4 / 71 (5.63%)	8 / 65 (12.31%)
occurrences (all)	6	4	8
Hypophosphataemia			
subjects affected / exposed	5 / 68 (7.35%)	5 / 71 (7.04%)	6 / 65 (9.23%)
occurrences (all)	5	5	6
Hypocalcaemia			
subjects affected / exposed	6 / 68 (8.82%)	7 / 71 (9.86%)	2 / 65 (3.08%)
occurrences (all)	6	7	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 November 2014	The following changes were made at the request of the USA Food and Drug Administration: the inclusion criteria for bilirubin was reduced to 1 × ULN, >Grade 2 pulmonary hypertension was added as a treatment termination criteria, a section was added regarding the role of the DSMB and clarifying the data that they would review and the sample informed consent was revised to clarify that subjects received 6 doses of demcizumab or placebo during each of the two 70-day truncated courses of therapy and that subjects might receive less intensive gemcitabine/Abraxane therapy than if they were not on the study due to demcizumab toxicity.
10 February 2015	The requirement for mandatory FFPE (either from archival tissue or from a fresh core biopsy) was removed and instead FFPE was only to be collected if available, i.e., subjects who did not have archival tissue were not undergo a core biopsy to obtain fresh tumor tissue. In addition, the requirement for subjects who had 2 BNP values > 100 pg/mL or 1 value> 200 pg/mL to be referred to a cardiologist changed to state that such subjects would referred to a cardiologist if appropriate. Definitions were added to the protocol for "women of child-bearing potential" and "adequate contraception". Additional serum pregnancy tests were added every 56 days while on study, at the termination visit and at 56 and 112 days following the termination visit for women of child-bearing potential.
28 May 2015	The primary purpose of this amendment was to make the following modifications to the inclusion/exclusion criteria. Inclusion criterion #1 was modified to allow subjects with a cytologic diagnosis to be eligible. Exclusion criterion #6 was modified to provide a definition of clinically significant ascites. The previous exclusion criterion #7 was removed so that subjects with plastic biliary stents are eligible. The previous exclusion criterion #10 (now exclusion criterion #9) was modified to clarify that subjects with prior chest wall radiotherapy are excluded only if the radiation field involved the heart. The previous exclusion criterion #16 (now exclusion criterion #15) was modified to state that subjects on prophylactic doses of heparin, warfarin, factor Xa inhibitors, or other similar anticoagulates are eligible. In addition, Section 13 of the protocol was modified to clarify that the BNP measurement must be obtained on the Day of the demcizumab dosing and the result reviewed prior to dosing and the sample informed consent was modified to clarify the objectives of the study. In addition, modifications were made to clarify the appropriate radiologic assessments to be obtained.
31 March 2016	The primary purpose of this amendment was to change the method for analyzing the primary endpoint of PFS. The previous approach for the primary endpoint analysis involved comparing placebo/placebo arm to demcizumab/placebo arm and placebo/placebo arm to demcizumab/demcizumab arm, separately. This approach required that 80% of subject achieve the PFS endpoint (i.e., either progress or died). However, a blinded review of the data to date suggests that only about 69% of the subjects are having a PFS event. Thus, it appears that there may not be an adequate number of events at the end of the study to conduct the PFS analysis initially described in the protocol. Thus, the method for this analysis has been modified to compare the placebo/placebo arm to a pooled dataset of the demcizumab/placebo arm and demcizumab/demcizumab arm, which requires a lower percentage of subjects to achieve a PFS endpoint. In addition, the wording of the study objectives and endpoints were modified to account for this modification. A statement that standard of tests performed prior to the informed consent date may be used for screening purposes if they were done within 28 days of Day 0. Also, wording was added to allow the BNP to be drawn the day prior to dosing at a site if approved by the sponsor.

19 December 2016	The primary purpose of this amendment was to add 2 additional analyses of overall survival to be conducted on all deaths through 01 June 2017 and 01 November 2017, respectively. In addition, the protocol was modified to state that subjects in long-term follow-up would have their survival status updated every 3 months or sooner at the request of the Sponsor. In addition, changes were made to the Abraxane/gemcitabine dosage modification section to: - Delete the statement that subjects having their gemcitabine/Abraxane therapy held for 21 days due to drug related toxicity should have their gemcitabine and Abraxane stopped - To add a statement that subjects who had undergone 2 dose reductions of gemcitabine/Abraxane and still were unable to tolerate that treatment could receive gemcitabine/Abraxane on Days 1 and 15 (i.e., omit Day 8) of each 28-day cycle

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported