



Clinical trial results:

A prospective randomised Phase III trial to evaluate optimal treatment duration of first-line bevacizumab in combination with carboplatin and paclitaxel in patients with primary epithelial ovarian, fallopian tube or peritoneal cancer.

Summary

EudraCT number	2011-001015-32
Trial protocol	DE FR FI NO DK SE
Global end of trial date	26 November 2020

Results information

Result version number	v1 (current)
This version publication date	21 July 2022
First version publication date	21 July 2022
Summary attachment (see zip file)	OVAR17_E3-Synopse_V01F_2021-11- (OVAR17_E3-Synopse_V01F_2021-11-09_signed.pdf)

Trial information

Trial identification

Sponsor protocol code	AGO-OVAR17
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01462890
WHO universal trial number (UTN)	-
Other trial identifiers	GINECO OV118: ENGOT Ov-15 Trial

Notes:

Sponsors

Sponsor organisation name	AGO Research GmbH
Sponsor organisation address	Kaiser-Friedrich-Ring 71, Wiesbaden, Germany, 65185
Public contact	Study Office, AGO Research GmbH, 0049 6118804 670, gelser@ago-ovar.de
Scientific contact	Study Office, AGO Research GmbH, 0049 6118804 670, gelser@ago-ovar.de

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	07 January 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare progression-free survival (PFS) (by RECIST v1.1, clinical or symptomatic) of patients randomized to front-line paclitaxel/carboplatin with bevacizumab for 15 months or 30 months.

Protection of trial subjects:

The study consisted of a screening/baseline period, a treatment period and a posttreatment or follow-up period.

Background therapy:

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Evidence for comparator:

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Actual start date of recruitment	01 July 2011
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	Norway: 12
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Finland: 14
Country: Number of subjects enrolled	France: 126
Country: Number of subjects enrolled	Germany: 764
Worldwide total number of subjects	927
EEA total number of subjects	927

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)	575
From 65 to 84 years	350
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of a screening/baseline period, a treatment period and a posttreatment or follow-up period.

Period 1

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

Arms

Are arms mutually exclusive? Yes

Arm title Standard arm

Arm description:

Bevacizumab, Paclitaxel, Carboplatin

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

Dosage and administration details:

15 mg/kg on day 1 every 3 weeks (together with chemotherapy treatment) up to and including cycle 21 or 22

Arm title Experimental arm

Arm description:

Bevacizumab, Paclitaxel, Carboplatin

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

Dosage and administration details:

15 mg/kg on day 1 every 3 weeks (together with chemotherapy treatment) up to and including cycle 43 or 44

Number of subjects in period 1	Standard arm	Experimental arm
Started	464	463
Completed	448	442
Not completed	16	21
Consent withdrawn by subject	7	5

Disease progression	1	-
Adverse event, non-fatal	4	4
Death	2	4
Another urgent surgery	1	-
Refused treatment	-	2
Intercurrent illness	1	4
Further therapy outside study (sponsor decision)	-	1
Incomplete wound healing (sponsor decision)	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall trial
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Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	927	927	
Age categorical			
female patients 18 years and older			
Units: Subjects			
Adults (18-64 years)	575	575	
From 65-84 years	350	350	
85 years and over	2	2	
Gender categorical			
Units: Subjects			
Female	927	927	
Male	0	0	

End points

End points reporting groups

Reporting group title	Standard arm
Reporting group description:	
Bevacizumab, Paclitaxel, Carboplatin	
Reporting group title	Experimental arm
Reporting group description:	
Bevacizumab, Paclitaxel, Carboplatin	

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description:	
End point type	Primary
End point timeframe:	
Progression-free survival (PFS) is defined as the time from the date of randomization to investigator assessed disease progression.	

End point values	Standard arm	Experimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	464	463		
Units: months				
number (not applicable)	24.2	26.0		

Statistical analyses

Statistical analysis title	Primary statistical analysis
Comparison groups	Standard arm v Experimental arm
Number of subjects included in analysis	927
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.15

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events occurring during the clinical trial or within 30 days after treatment discontinuation

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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Reporting groups

Reporting group title	Standard arm
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Reporting group description: -

Reporting group title	Experimental arm
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Reporting group description: -

Serious adverse events	Standard arm	Experimental arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	199 / 448 (44.42%)	204 / 442 (46.15%)	
number of deaths (all causes)	257	277	
number of deaths resulting from adverse events	8	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to kidney			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic cerebellar degeneration			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	2 / 448 (0.45%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 448 (0.67%)	3 / 442 (0.68%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	11 / 448 (2.46%)	16 / 442 (3.62%)	
occurrences causally related to treatment / all	12 / 12	17 / 17	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 448 (0.00%)	4 / 442 (0.90%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypertensive emergency			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocele			
subjects affected / exposed	7 / 448 (1.56%)	9 / 442 (2.04%)	
occurrences causally related to treatment / all	0 / 8	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	2 / 448 (0.45%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 448 (0.00%)	4 / 442 (0.90%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Bladder catheter removal			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder catheter replacement			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central venous catheterisation			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 448 (0.00%)	3 / 442 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	3 / 448 (0.67%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	2 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Device dislocation			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device leakage			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device occlusion			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 448 (0.67%)	5 / 442 (1.13%)	
occurrences causally related to treatment / all	0 / 4	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	20 / 448 (4.46%)	20 / 442 (4.52%)	
occurrences causally related to treatment / all	3 / 26	7 / 32	
deaths causally related to treatment / all	1 / 1	1 / 1	
Hernia obstructive			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	2 / 448 (0.45%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	2 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site reaction			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			

subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	11 / 448 (2.46%)	16 / 442 (3.62%)	
occurrences causally related to treatment / all	0 / 12	4 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis in device			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 448 (0.45%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	2 / 448 (0.45%)	3 / 442 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	3 / 448 (0.67%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			

Female genital tract fistula subjects affected / exposed	3 / 448 (0.67%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea subjects affected / exposed	6 / 448 (1.34%)	11 / 442 (2.49%)	
occurrences causally related to treatment / all	2 / 6	4 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion subjects affected / exposed	4 / 448 (0.89%)	6 / 442 (1.36%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial hypertension subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism subjects affected / exposed	6 / 448 (1.34%)	7 / 442 (1.58%)	
occurrences causally related to treatment / all	3 / 6	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory disorder			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety disorder			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystoscopy			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Neutrophil count decreased subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femoral neck fracture subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder injury subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal injury subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incisional hernia			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 448 (0.22%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			

subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urostomy complication			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 448 (0.45%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cardiac failure		
subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)
occurrences causally related to treatment / all	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiomyopathy		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiovascular disorder		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Left ventricular dysfunction		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial infarction		
subjects affected / exposed	0 / 448 (0.00%)	3 / 442 (0.68%)
occurrences causally related to treatment / all	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pericardial effusion		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Sinus tachycardia		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Supraventricular tachycardia		

subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Convulsion			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 448 (0.22%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	5 / 448 (1.12%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	3 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial venous sinus thrombosis			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve compression			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			

subjects affected / exposed	0 / 448 (0.00%)	3 / 442 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	2 / 448 (0.45%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 448 (0.45%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 448 (1.34%)	5 / 442 (1.13%)	
occurrences causally related to treatment / all	2 / 7	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	9 / 448 (2.01%)	4 / 442 (0.90%)	
occurrences causally related to treatment / all	2 / 9	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	4 / 448 (0.89%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	2 / 448 (0.45%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Lens dislocation			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	2 / 448 (0.45%)	3 / 442 (0.68%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	17 / 448 (3.79%)	16 / 442 (3.62%)	
occurrences causally related to treatment / all	3 / 21	3 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal pain upper		
subjects affected / exposed	1 / 448 (0.22%)	6 / 442 (1.36%)
occurrences causally related to treatment / all	0 / 1	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal wall haematoma		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Acute abdomen		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Anal fistula		
subjects affected / exposed	4 / 448 (0.89%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	4 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ascites		
subjects affected / exposed	10 / 448 (2.23%)	2 / 442 (0.45%)
occurrences causally related to treatment / all	0 / 17	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Bowel movement irregularity		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Colonic fistula		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Colonic obstruction		

subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	6 / 448 (1.34%)	8 / 442 (1.81%)	
occurrences causally related to treatment / all	0 / 6	1 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diaphragmatic hernia			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	9 / 448 (2.01%)	6 / 442 (1.36%)	
occurrences causally related to treatment / all	3 / 9	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal stenosis			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocutaneous fistula			

subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Faecal incontinence		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Faecaloma		
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric perforation		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastritis		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal disorder		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal haemorrhage		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal motility disorder		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrooesophageal reflux disease		

subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileal fistula			
subjects affected / exposed	2 / 448 (0.45%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	9 / 448 (2.01%)	11 / 442 (2.49%)	
occurrences causally related to treatment / all	3 / 9	0 / 11	
deaths causally related to treatment / all	1 / 1	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal fistula			
subjects affected / exposed	2 / 448 (0.45%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			

subjects affected / exposed	1 / 448 (0.22%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery embolism			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nausea			
subjects affected / exposed	1 / 448 (0.22%)	5 / 442 (1.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral cavity fistula			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sigmoiditis			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	15 / 448 (3.35%)	7 / 442 (1.58%)	
occurrences causally related to treatment / all	2 / 15	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 448 (0.22%)	8 / 442 (1.81%)	
occurrences causally related to treatment / all	0 / 1	3 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Bladder disorder			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	7 / 448 (1.56%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	2 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	1 / 448 (0.22%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	3 / 448 (0.67%)	6 / 442 (1.36%)	
occurrences causally related to treatment / all	3 / 3	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelocaliectasis			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			

subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary incontinence			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	2 / 448 (0.45%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract disorder			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 448 (0.00%)	3 / 442 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 448 (0.45%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	2 / 448 (0.45%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatic disorder			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			

subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall abscess			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall infection			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess of salivary gland			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 448 (0.00%)	2 / 442 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	3 / 448 (0.67%)	3 / 442 (0.68%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	5 / 448 (1.12%)	4 / 442 (0.90%)	
occurrences causally related to treatment / all	1 / 5	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			

subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	2 / 448 (0.45%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Helicobacter gastritis			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected cyst			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected lymphocele			

subjects affected / exposed	5 / 448 (1.12%)	6 / 442 (1.36%)
occurrences causally related to treatment / all	0 / 5	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Infection		
subjects affected / exposed	2 / 448 (0.45%)	5 / 442 (1.13%)
occurrences causally related to treatment / all	1 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle abscess		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oral herpes		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Otitis media		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pelvic abscess		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritonsillar abscess		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	0 / 448 (0.00%)	4 / 442 (0.90%)
occurrences causally related to treatment / all	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative wound infection		

subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Psoas abscess		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis		
subjects affected / exposed	1 / 448 (0.22%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	2 / 448 (0.45%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	1 / 2	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0
Skin infection		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Subcutaneous abscess		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Upper respiratory tract infection		
subjects affected / exposed	1 / 448 (0.22%)	2 / 442 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Urethritis		
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection		

subjects affected / exposed	7 / 448 (1.56%)	6 / 442 (1.36%)	
occurrences causally related to treatment / all	2 / 7	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	2 / 448 (0.45%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal abscess			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture rupture			
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Wound haemorrhage			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 448 (0.45%)	5 / 442 (1.13%)	
occurrences causally related to treatment / all	0 / 2	3 / 6	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypercalcaemia			

subjects affected / exposed	1 / 448 (0.22%)	0 / 442 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypokalaemia		
subjects affected / exposed	0 / 448 (0.00%)	1 / 442 (0.23%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hyponatraemia		
subjects affected / exposed	3 / 448 (0.67%)	2 / 442 (0.45%)
occurrences causally related to treatment / all	1 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0

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

Non-serious adverse events	Standard arm	Experimental arm
Total subjects affected by non-serious adverse events		
subjects affected / exposed	445 / 448 (99.33%)	439 / 442 (99.32%)
Vascular disorders		
Hot flush		
subjects affected / exposed	33 / 448 (7.37%)	35 / 442 (7.92%)
occurrences (all)	61	62
Hypertension		
subjects affected / exposed	168 / 448 (37.50%)	232 / 442 (52.49%)
occurrences (all)	546	783
General disorders and administration site conditions		
Asthenia		
subjects affected / exposed	40 / 448 (8.93%)	53 / 442 (11.99%)
occurrences (all)	91	101
Fatigue		
subjects affected / exposed	204 / 448 (45.54%)	208 / 442 (47.06%)
occurrences (all)	421	447
General physical health deterioration		
subjects affected / exposed	23 / 448 (5.13%)	24 / 442 (5.43%)
occurrences (all)	34	36
Mucosal inflammation		

subjects affected / exposed occurrences (all)	67 / 448 (14.96%) 114	65 / 442 (14.71%) 111	
Oedema subjects affected / exposed occurrences (all)	20 / 448 (4.46%) 28	35 / 442 (7.92%) 53	
Oedema peripheral subjects affected / exposed occurrences (all)	26 / 448 (5.80%) 30	35 / 442 (7.92%) 47	
Pain subjects affected / exposed occurrences (all)	45 / 448 (10.04%) 71	28 / 442 (6.33%) 59	
Pyrexia subjects affected / exposed occurrences (all)	47 / 448 (10.49%) 69	53 / 442 (11.99%) 66	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	15 / 448 (3.35%) 22	32 / 442 (7.24%) 55	
Hypersensitivity subjects affected / exposed occurrences (all)	29 / 448 (6.47%) 33	25 / 442 (5.66%) 31	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	23 / 448 (5.13%) 28	40 / 442 (9.05%) 47	
Dysphonia subjects affected / exposed occurrences (all)	19 / 448 (4.24%) 25	35 / 442 (7.92%) 41	
Dyspnoea subjects affected / exposed occurrences (all)	82 / 448 (18.30%) 119	88 / 442 (19.91%) 133	
Epistaxis subjects affected / exposed occurrences (all)	86 / 448 (19.20%) 106	101 / 442 (22.85%) 150	
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	23 / 448 (5.13%) 27	23 / 442 (5.20%) 31	
Insomnia subjects affected / exposed occurrences (all)	47 / 448 (10.49%) 71	41 / 442 (9.28%) 60	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	18 / 448 (4.02%) 32	27 / 442 (6.11%) 54	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	30 / 448 (6.70%) 43	26 / 442 (5.88%) 40	
Dysgeusia subjects affected / exposed occurrences (all)	23 / 448 (5.13%) 29	34 / 442 (7.69%) 40	
Headache subjects affected / exposed occurrences (all)	70 / 448 (15.63%) 124	95 / 442 (21.49%) 160	
Neuropathy peripheral subjects affected / exposed occurrences (all)	49 / 448 (10.94%) 90	47 / 442 (10.63%) 90	
Paraesthesia subjects affected / exposed occurrences (all)	40 / 448 (8.93%) 48	47 / 442 (10.63%) 71	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	144 / 448 (32.14%) 263	129 / 442 (29.19%) 284	
Polyneuropathy subjects affected / exposed occurrences (all)	81 / 448 (18.08%) 141	98 / 442 (22.17%) 182	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	83 / 448 (18.53%) 202	87 / 442 (19.68%) 196	
Leukopenia			

subjects affected / exposed occurrences (all)	37 / 448 (8.26%) 111	49 / 442 (11.09%) 138	
Neutropenia subjects affected / exposed occurrences (all)	63 / 448 (14.06%) 165	80 / 442 (18.10%) 219	
Thrombocytopenia subjects affected / exposed occurrences (all)	36 / 448 (8.04%) 79	39 / 442 (8.82%) 90	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	21 / 448 (4.69%) 25	27 / 442 (6.11%) 36	
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	92 / 448 (20.54%) 132	96 / 442 (21.72%) 152	
Abdominal pain upper subjects affected / exposed occurrences (all)	47 / 448 (10.49%) 80	60 / 442 (13.57%) 82	
Constipation subjects affected / exposed occurrences (all)	170 / 448 (37.95%) 282	169 / 442 (38.24%) 322	
Diarrhoea subjects affected / exposed occurrences (all)	141 / 448 (31.47%) 291	117 / 442 (26.47%) 256	
Nausea subjects affected / exposed occurrences (all)	202 / 448 (45.09%) 386	180 / 442 (40.72%) 348	
Stomatitis subjects affected / exposed occurrences (all)	62 / 448 (13.84%) 93	72 / 442 (16.29%) 106	
Vomiting subjects affected / exposed occurrences (all)	111 / 448 (24.78%) 171	88 / 442 (19.91%) 135	
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	288 / 448 (64.29%) 354	294 / 442 (66.52%) 364	
Rash subjects affected / exposed occurrences (all)	20 / 448 (4.46%) 20	31 / 442 (7.01%) 39	
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	42 / 448 (9.38%) 95	73 / 442 (16.52%) 262	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	127 / 448 (28.35%) 225	138 / 442 (31.22%) 295	
Back pain subjects affected / exposed occurrences (all)	35 / 448 (7.81%) 38	53 / 442 (11.99%) 69	
Bone pain subjects affected / exposed occurrences (all)	47 / 448 (10.49%) 75	46 / 442 (10.41%) 68	
Musculoskeletal pain subjects affected / exposed occurrences (all)	22 / 448 (4.91%) 39	36 / 442 (8.14%) 54	
Myalgia subjects affected / exposed occurrences (all)	84 / 448 (18.75%) 149	91 / 442 (20.59%) 171	
Pain in extremity subjects affected / exposed occurrences (all)	59 / 448 (13.17%) 97	59 / 442 (13.35%) 85	
Infections and infestations Cystitis subjects affected / exposed occurrences (all)	54 / 448 (12.05%) 88	49 / 442 (11.09%) 92	
Nasopharyngitis subjects affected / exposed occurrences (all)	47 / 448 (10.49%) 59	63 / 442 (14.25%) 82	

Urinary tract infection subjects affected / exposed occurrences (all)	66 / 448 (14.73%) 102	85 / 442 (19.23%) 133	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	30 / 448 (6.70%) 58	39 / 442 (8.82%) 65	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 December 2011	New Protocol V03 F (21/11/2011): Specification of exclusion criteria no. 22, Additions regarding the second opinion pathology for patients from France, Update of Patient Information and Informed Consent Form
27 March 2013	New Protokoll V05 F (14/03/2013): Update of the statistical considerations including increase of the number of patients to 900, Update of Patient Information and Informed Consent Form
19 July 2013	Update of Patient Information and Informed Consent Form due to "Roter-Hand-Brief" of 15.05.2013
06 January 2015	Additional Patient Information and Informed Consent Form due to changes in the German Summary of Product Characteristics Avastin 09/2014
28 December 2016	New Protocol V06 F (15/11/2016): Wording for the efficacy follow-up period has been corrected or rather adjusted
24 September 2020	Amendment No. 1 (31/08/2020) to Protocol V06 F: Removes PFS events as a condition of the timing of the data cutoff for primary analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported