Clinical trial results:
A Phase III Open Label, Randomized, 2 Arm Study of Ixabepilone Administered Every 21 Days Versus Paclitaxel or Doxorubicin Administered Every 21 Days in Women with Advanced Endometrial Cancer Who Have Previously Been Treated with Chemotherapy.

Summary

EudraCT number	2008-007167-16
Trial protocol	GB BE IT ES FR SE GR DK HU FI CZ
Global end of trial date	08 December 2013

Results information

Result version number	v1 (current)
This version publication date	18 August 2016
First version publication date	18 August 2016

Trial information

Trial identification

Sponsor protocol code	CA163-196

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00883116
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to investigate whether administration of ixabepilone results in superior outcome as assessed by overall survival compared with that achieved with standard chemotherapy (paclitaxel or doxorubicin) in women with advanced endometrial cancer that has progressed following first-line chemotherapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2009
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: 11
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Sweden: 16
Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Belgium: 22
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Denmark: 16
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Greece: 16
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Italy: 47
Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Brazil: 25
Country: Number of subjects enrolled	Canada: 56
Country: Number of subjects enrolled	Mexico: 21
Country: Number of subjects enrolled	Peru: 23
Country: Number of subjects enrolled	Russian Federation: 51
Country: Number of subjects enrolled	United States: 154

Worldwide total number of subjects	551
EEA total number of subjects	206

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)	296
From 65 to 84 years	252
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 496 subjects were randomised in the study and 487 subjects were treated (248 subjects in the ixabepilone arm and 239 subjects in the control arm).

Period 1

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

Blinding implementation details:

The study was open label, hence blinding was not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ixabepilone, 40 mg/m^2, IV

Arm description:

Subjects received ixabepilone, 40 mg/m^2, intravenously (IV) over 3 hours every 21 days until unacceptable toxicity or disease progression.

Arm type	Experimental
Investigational medicinal product name	Ixabepilone
Investigational medicinal product code	BMS-247550
Other name	Ixempra
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ixabepilone 40 mg/m^2 IV infusion over 3 hours, every 21 days until unacceptable toxicity or disease progression.

Arm title	Control chemotherapy

Arm description:

Subjects received either paclitaxel, 175 mg/m^2 given IV over 3 hours, or per institutional guidelines but not exceeding 3 hours, every 21 days until disease progression or unacceptable toxicity or doxorubicin, 60 mg/m^2 given IV per institutional guidelines every 21 days, depending on the prior therapy received, until disease progression, unacceptable toxicity, or cumulative dose of 500 mg/m^2.

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	Adriacin, Adriamycin PFS/RDF, Adriblastina, Adriablastine, Adrimedac, Doxorubin, Farmiblasti, Rubexna, DOXO-CELL, Doxolem
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin 60 mg/m^2 IV infusion either in a peripheral or central venous line, every 21 days until unacceptable toxicity or disease progression.

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	Taxol, Anzatax, Asotax, Bristaxol Praxel, Taxol Konzentrat, F1-106
Pharmaceutical forms	Infusion

Routes of administration	Intravenous use

Dosage and administration details:

Paclitaxel 175 mg/m^2 IV infusion over 3 hours, every 21 days until unacceptable toxicity or disease progression.

Number of subjects in period 1[1]	Ixabepilone, 40 mg/m^2, IV	Control chemotherapy
Started	248	248
Completed	39	29
Not completed	209	219
No longer meet study criteria	2	1
Consent withdrawn by subject	1	2
Disease progression	130	127
Study drug toxicity	36	16
Death	6	2
Subject request to discontinue study treatment	13	5
Maximum clinical benefit	13	46
Adverse event unrelated to study drug	5	10
Never treated	-	9
Lost to follow-up	-	1
unspecified	3	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 551 subjects that were enrolled, 496 subjects were randomised in the study and 487 subjects were treated (248 subjects in the ixabepilone arm and 239 subjects in the control arm).

Baseline characteristics

Reporting groups	
Reporting group title	Ixabepilone, 40 mg/m^2, IV
Reporting group description:	
Subjects received ixabepilone, 40 mg/m^2, intravenously (IV) over 3 hours every 21 days until unacceptable toxicity or disease progression.	
Reporting group title	Control chemotherapy
Reporting group description:	
Subjects received either paclitaxel, 175 mg/m^2 given IV over 3 hours, or per institutional guidelines but not exceeding 3 hours, every 21 days until disease progression or unacceptable toxicity or doxorubicin, 60 mg/m^2 given IV per institutional guidelines every 21 days, depending on the prior therapy received, until disease progression, unacceptable toxicity, or cumulative dose of 500 mg/m^2.	

Reporting group values	Ixabepilone, 40 mg/m^2, IV	Control chemotherapy	Total
Number of subjects	248	248	496
Age categorical Units: Subjects			
<65 years	126	139	265
>=65 years	122	109	231
Age continuous Units: years			
median	64	64	
full range (min-max)	39 to 86	33 to 88	-
Gender categorical Units: Subjects			
Female	248	248	496
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	215	213	428
Black or African American	12	18	30
Asian	6	5	11
Other	12	12	24
American Indian or Alaska Native	3	0	3
Karnofsky Performance Scale Index Status			
This scale classifies subjects by functional impairment. The lower the Karnofsky score, the more impaired the subject is. 100=No complaints; 90=Normal activity; 80=Normal activity with effort; 70=Cares for self but unable to carry on normal activity or to do active work; 60=Requires occasional assistance, but is able to care for most personal needs; 50=Requires considerable assistance; 40=Disabled; requires special care; 30=Severely disabled hospitalization indicated; 20=Very sick; hospital admission necessary; 10=Fatal processes progressing rapidly; 0=Death.			
Units: Subjects			
100	86	86	172
90	95	79	174
80	48	64	112
70	19	16	35
Fewer than 70	0	2	2
Not reported	0	1	1

End points

End points reporting groups

Reporting group title	Ixabepilone, 40 mg/m^2, IV

Reporting group description:

Subjects received ixabepilone, 40 mg/m^2, intravenously (IV) over 3 hours every 21 days until unacceptable toxicity or disease progression.

Reporting group title	Control chemotherapy

Reporting group description:

Subjects received either paclitaxel, 175 mg/m^2 given IV over 3 hours, or per institutional guidelines but not exceeding 3 hours, every 21 days until disease progression or unacceptable toxicity or doxorubicin, 60 mg/m^2 given IV per institutional guidelines every 21 days, depending on the prior therapy received, until disease progression, unacceptable toxicity, or cumulative dose of 500 mg/m^2.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Survival was defined as the time from the date of randomisation until the date of death. If the subject did not die, OS was censored on the last date he or she was known to be alive. The analysis was performed on all the randomised subjects.

End point type	Primary

End point timeframe:

Date of randomization to date of death or last date censored to up to approximately 26 months

End point values	Ixabepilone, 40 mg/m^2, IV	Control chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	248		
Units: Month				
median (confidence interval 95%)	10.9 (8.5 to 12.7)	12.3 (10.7 to 15.4)		

Statistical analyses

Statistical analysis title	Overall survival comparison
Comparison groups	Control chemotherapy v Ixabepilone, 40 mg/m^2, IV
Number of subjects included in analysis	496
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0397
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.01
upper limit	1.74

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

Progression-free survival was defined as the time from randomization to the date of documented disease progression. Subjects who died without a reported prior progression were considered to have progressed on the date of their death. Those who did not progress or die were censored on the date of their last tumor assessment. Subjects who did not have any on-study tumor assessments were censored on the date they were randomized. Measurable disease was present if the subject had 1 or more measurable lesions. The analysis was performed on all the subjects with measurable disease at randomisation.

End point type	Secondary

End point timeframe:

Date of randomization up to disease progression or death (or date of last tumor assessment for those who did not die or progress) up to approximately 22 months

End point values	Ixabepilone, 40 mg/m^2, IV	Control chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Months				
median (confidence interval 95%)	3.4 (2.8 to 4.2)	4 (2.7 to 4.3)		

Statistical analyses

Statistical analysis title	Progression-free Survival Comparison
Comparison groups	Ixabepilone, 40 mg/m^2, IV v Control chemotherapy
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8011
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.29

Secondary: Best Overall Response Rate

End point title	Best Overall Response Rate

End point description:

Best overall response rate was defined as the number of subjects whose best response was either partial response (PR) or complete response (CR) divided by the number of subjects in the treatment group. Overall tumor response was based on an integration of the evaluation of target, non target, and new lesions. CR=Disappearance of all clinical and radiologic evidence of target lesions. PR=At least 30% reduction in the sum of diameters of all target lesions, taking as reference the baseline study measurement. Changes in tumor measurements need not be confirmed by repeat measurements performed after the criteria for response were first met. The analysis was performed on all randomised subjects with measurable disease.

End point type	Secondary

End point timeframe:

Date of randomization and every 6 weeks to end of treatment (9 cycles, or approximately Day 189)

End point values	Ixabepilone, 40 mg/m^2, IV	Control chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: Percentage of subjects				
number (confidence interval 95%)	15.2 (10.8 to 20.6)	15.7 (11.2 to 21.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With a Serious Adverse Event (SAE), an SAE Related to Study Drug, Death as Outcome, a Peripheral Neuropathy Adverse Event (AE), a Grade 3 or Higher AE, and an AE Related to Study Drug

End point title	Number of Subjects With a Serious Adverse Event (SAE), an SAE Related to Study Drug, Death as Outcome, a Peripheral Neuropathy Adverse Event (AE), a Grade 3 or Higher AE, and an AE Related to Study Drug

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. Related to study drug=having certain, probable, possible, or missing relationship to study drug. Grade (Gr) 1=Mild, Gr 2=Moderate, Gr 3=Severe, Gr 4=Life-threatening or disabling, Gr 5=Death. The analysis was performed on all subjects who received at least 1 dose of ixabepilone.

End point type	Secondary

End point timeframe:

Baseline up to disease progression or until study related toxicities resolve to baseline

End point values	Ixabepilone, 40 mg/m^2, IV	Control chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	248	239		
Units: subjects				
SAEs	89	70		
Any SAE related to study drug	43	29		
Deaths	121	95		
Any AE related to study drug	223	215		
Any AE leading to study drug discontinuation	49	37		
Any peripheral neuropathy AE	108	62		
Any Grade 3 or higher AE	160	148		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to disease progression or until study related toxicities resolve to baseline	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Ixabepilone, 40 mg/m^2, IV
Reporting group description:	
Subjects received ixabepilone, 40 milligram per square meter (mg/m^2), intravenously (IV) over 3 hours every 21 days until unacceptable toxicity or disease progression.	
Reporting group title	Doxorubicin, 60 mg/m^2, IV
Reporting group description:	
Doxorubicin 60 mg/m^2 IV infusion either in a peripheral or central venous line, every 21 days until unacceptable toxicity or disease progression.	
Reporting group title	Paclitaxel, 175 mg/m^2, IV
Reporting group description:	
Paclitaxel 175 mg/m^2 IV infusion over 3 hours, every 21 days until unacceptable toxicity or disease progression.	

Serious adverse events	Ixabepilone, 40 mg/m^2, IV	Doxorubicin, 60 mg/m^2, IV	Paclitaxel, 175 mg/m^2, IV
Total subjects affected by serious adverse events			
subjects affected / exposed	89 / 248 (35.89%)	59 / 171 (34.50%)	11 / 68 (16.18%)
number of deaths (all causes)	121	76	19
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Neoplasm malignant			
subjects affected / exposed	4 / 248 (1.61%)	5 / 171 (2.92%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 5	0 / 0
Malignant pleural effusion			

subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Metastases to central nervous system			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 248 (0.40%)	4 / 171 (2.34%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Hypertension			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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			
Asthenia			
subjects affected / exposed	3 / 248 (1.21%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device malfunction			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fatigue			
subjects affected / exposed	4 / 248 (1.61%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Mucosal inflammation			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Oedema			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Pain			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Performance status decreased			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Pyrexia			
subjects affected / exposed	4 / 248 (1.61%)	4 / 171 (2.34%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	3 / 4	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			

subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Death			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	2 / 248 (0.81%)	1 / 171 (0.58%)	0 / 68 (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
Dyspnoea exertional			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Apnoea			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Dyspnoea			
subjects affected / exposed	0 / 248 (0.00%)	6 / 171 (3.51%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haemoptysis			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Pleural effusion			
subjects affected / exposed	3 / 248 (1.21%)	1 / 171 (0.58%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Pulmonary embolism			
subjects affected / exposed	3 / 248 (1.21%)	6 / 171 (3.51%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 3	1 / 6	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Respiratory failure			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Confusional state			
subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	0 / 68 (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
Depression			

subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Blood creatinine increased			
subjects affected / exposed	3 / 248 (1.21%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular filtration rate decreased			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Haemoglobin decreased			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 248 (0.00%)	2 / 171 (1.17%)	0 / 68 (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
Neutrophil count decreased			
subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	0 / 68 (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
White blood cell count decreased			

subjects affected / exposed	2 / 248 (0.81%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoalbuminaemia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Hypocalcaemia			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Hypokalaemia			
subjects affected / exposed	3 / 248 (1.21%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypomagnesaemia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Hyponatraemia			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (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
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
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			
Hip fracture			

subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Humerus fracture			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Incorrect dose administered			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Overdose			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (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
Cardiac failure congestive			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Cardiac tamponade			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Cardio-respiratory arrest			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Intracardiac thrombus			

subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Right ventricular failure			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Tachyarrhythmia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Tachycardia			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 248 (0.81%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral motor neuropathy			

subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 248 (2.02%)	7 / 171 (4.09%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	5 / 5	4 / 7	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	10 / 248 (4.03%)	10 / 171 (5.85%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	11 / 11	9 / 10	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	3 / 248 (1.21%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	6 / 248 (2.42%)	4 / 171 (2.34%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	8 / 8	3 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	0 / 68 (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
Abdominal pain			
subjects affected / exposed	4 / 248 (1.61%)	6 / 171 (3.51%)	2 / 68 (2.94%)
occurrences causally related to treatment / all	0 / 6	1 / 7	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ascites			
subjects affected / exposed	3 / 248 (1.21%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Constipation			
subjects affected / exposed	4 / 248 (1.61%)	4 / 171 (2.34%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 7	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Diarrhoea			
subjects affected / exposed	9 / 248 (3.63%)	2 / 171 (1.17%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	5 / 10	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Dysphagia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Enterovesical fistula			

subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Gastrointestinal obstruction			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Haematemesis			
subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	0 / 68 (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
Ileus			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 248 (0.40%)	3 / 171 (1.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	2 / 248 (0.81%)	2 / 171 (1.17%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Large intestinal haemorrhage			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Nausea			
subjects affected / exposed	8 / 248 (3.23%)	7 / 171 (4.09%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	5 / 12	5 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Oesophagitis			

subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Rectal haemorrhage			
subjects affected / exposed	1 / 248 (0.40%)	2 / 171 (1.17%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Rectal obstruction			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 248 (0.40%)	2 / 171 (1.17%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Stomatitis			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Vomiting			
subjects affected / exposed	9 / 248 (3.63%)	4 / 171 (2.34%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	8 / 14	1 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Skin and subcutaneous tissue disorders			
Intertrigo			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Renal and urinary disorders			
Anuria			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chromaturia			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Haemorrhage urinary tract			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Hydronephrosis			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (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
Renal failure			
subjects affected / exposed	1 / 248 (0.40%)	1 / 171 (0.58%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Renal failure acute			
subjects affected / exposed	2 / 248 (0.81%)	2 / 171 (1.17%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 2	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Ureteric obstruction			

subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 248 (0.00%)	2 / 171 (1.17%)	0 / 68 (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
Urinary tract obstruction			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Haematuria			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (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
Pain in extremity			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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			
Cellulitis			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium bacteraemia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Device related infection			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 248 (0.00%)	2 / 171 (1.17%)	0 / 68 (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
Infectious peritonitis			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Pneumonia			

subjects affected / exposed	0 / 248 (0.00%)	3 / 171 (1.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory moniliasis			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Pyelonephritis			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
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 chronic			
subjects affected / exposed	0 / 248 (0.00%)	0 / 171 (0.00%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salmonellosis			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Sepsis			
subjects affected / exposed	3 / 248 (1.21%)	2 / 171 (1.17%)	1 / 68 (1.47%)
occurrences causally related to treatment / all	3 / 3	1 / 2	1 / 1
deaths causally related to treatment / all	3 / 3	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	0 / 248 (0.00%)	1 / 171 (0.58%)	0 / 68 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Urinary tract infection			

subjects affected / exposed	4 / 248 (1.61%)	3 / 171 (1.75%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Candidiasis			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 248 (0.81%)	0 / 171 (0.00%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	5 / 248 (2.02%)	5 / 171 (2.92%)	0 / 68 (0.00%)
occurrences causally related to treatment / all	3 / 5	1 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 2	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 248 (0.40%)	0 / 171 (0.00%)	0 / 68 (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

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

Non-serious adverse events	Ixabepilone, 40 mg/m^2, IV	Doxorubicin, 60 mg/m^2, IV	Paclitaxel, 175 mg/m^2, IV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	233 / 248 (93.95%)	160 / 171 (93.57%)	63 / 68 (92.65%)
Investigations			
Haemoglobin decreased			
subjects affected / exposed	13 / 248 (5.24%)	11 / 171 (6.43%)	3 / 68 (4.41%)
occurrences (all)	17	19	4
Weight decreased			
subjects affected / exposed	48 / 248 (19.35%)	28 / 171 (16.37%)	3 / 68 (4.41%)
occurrences (all)	52	31	3
Weight increased			

subjects affected / exposed	3 / 248 (1.21%)	2 / 171 (1.17%)	4 / 68 (5.88%)
occurrences (all)	3	2	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	24 / 248 (9.68%)	10 / 171 (5.85%)	1 / 68 (1.47%)
occurrences (all)	27	11	1
Dysgeusia			
subjects affected / exposed	23 / 248 (9.27%)	18 / 171 (10.53%)	1 / 68 (1.47%)
occurrences (all)	29	21	1
Headache			
subjects affected / exposed	19 / 248 (7.66%)	16 / 171 (9.36%)	0 / 68 (0.00%)
occurrences (all)	23	24	0
Neuropathy peripheral			
subjects affected / exposed	17 / 248 (6.85%)	3 / 171 (1.75%)	5 / 68 (7.35%)
occurrences (all)	17	3	5
Hypoaesthesia			
subjects affected / exposed	3 / 248 (1.21%)	1 / 171 (0.58%)	6 / 68 (8.82%)
occurrences (all)	4	1	8
Paraesthesia			
subjects affected / exposed	10 / 248 (4.03%)	3 / 171 (1.75%)	5 / 68 (7.35%)
occurrences (all)	16	3	6
Peripheral motor neuropathy			
subjects affected / exposed	12 / 248 (4.84%)	2 / 171 (1.17%)	5 / 68 (7.35%)
occurrences (all)	15	2	5
Peripheral sensory neuropathy			
subjects affected / exposed	79 / 248 (31.85%)	10 / 171 (5.85%)	29 / 68 (42.65%)
occurrences (all)	88	10	37
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	62 / 248 (25.00%)	46 / 171 (26.90%)	16 / 68 (23.53%)
occurrences (all)	83	59	17
Leukopenia			
subjects affected / exposed	35 / 248 (14.11%)	25 / 171 (14.62%)	6 / 68 (8.82%)
occurrences (all)	98	51	8
Lymphopenia			

subjects affected / exposed	7 / 248 (2.82%)	11 / 171 (6.43%)	0 / 68 (0.00%)
occurrences (all)	14	15	0
Thrombocytopenia			
subjects affected / exposed	16 / 248 (6.45%)	12 / 171 (7.02%)	2 / 68 (2.94%)
occurrences (all)	28	20	3
Neutropenia			
subjects affected / exposed	58 / 248 (23.39%)	68 / 171 (39.77%)	11 / 68 (16.18%)
occurrences (all)	106	127	16
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	39 / 248 (15.73%)	24 / 171 (14.04%)	11 / 68 (16.18%)
occurrences (all)	51	30	15
Fatigue			
subjects affected / exposed	125 / 248 (50.40%)	88 / 171 (51.46%)	21 / 68 (30.88%)
occurrences (all)	176	117	26
Mucosal inflammation			
subjects affected / exposed	21 / 248 (8.47%)	28 / 171 (16.37%)	0 / 68 (0.00%)
occurrences (all)	26	38	0
Oedema peripheral			
subjects affected / exposed	27 / 248 (10.89%)	20 / 171 (11.70%)	6 / 68 (8.82%)
occurrences (all)	27	21	7
Pyrexia			
subjects affected / exposed	17 / 248 (6.85%)	22 / 171 (12.87%)	4 / 68 (5.88%)
occurrences (all)	18	26	4
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	45 / 248 (18.15%)	24 / 171 (14.04%)	5 / 68 (7.35%)
occurrences (all)	52	26	7
Abdominal pain upper			
subjects affected / exposed	7 / 248 (2.82%)	14 / 171 (8.19%)	1 / 68 (1.47%)
occurrences (all)	11	17	2
Constipation			
subjects affected / exposed	77 / 248 (31.05%)	49 / 171 (28.65%)	7 / 68 (10.29%)
occurrences (all)	118	63	7
Dyspepsia			

subjects affected / exposed	17 / 248 (6.85%)	14 / 171 (8.19%)	0 / 68 (0.00%)
occurrences (all)	19	14	0
Diarrhoea			
subjects affected / exposed	76 / 248 (30.65%)	47 / 171 (27.49%)	8 / 68 (11.76%)
occurrences (all)	113	62	13
Nausea			
subjects affected / exposed	118 / 248 (47.58%)	101 / 171 (59.06%)	17 / 68 (25.00%)
occurrences (all)	190	148	30
Stomatitis			
subjects affected / exposed	16 / 248 (6.45%)	18 / 171 (10.53%)	1 / 68 (1.47%)
occurrences (all)	23	20	2
Vomiting			
subjects affected / exposed	73 / 248 (29.44%)	48 / 171 (28.07%)	8 / 68 (11.76%)
occurrences (all)	122	70	9
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	13 / 248 (5.24%)	2 / 171 (1.17%)	4 / 68 (5.88%)
occurrences (all)	13	2	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 248 (9.27%)	19 / 171 (11.11%)	5 / 68 (7.35%)
occurrences (all)	23	19	9
Dyspnoea			
subjects affected / exposed	37 / 248 (14.92%)	33 / 171 (19.30%)	8 / 68 (11.76%)
occurrences (all)	40	35	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	102 / 248 (41.13%)	63 / 171 (36.84%)	36 / 68 (52.94%)
occurrences (all)	103	65	36
Rash			
subjects affected / exposed	21 / 248 (8.47%)	7 / 171 (4.09%)	3 / 68 (4.41%)
occurrences (all)	25	7	4
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 248 (4.44%)	13 / 171 (7.60%)	1 / 68 (1.47%)
occurrences (all)	11	14	1

Insomnia			
subjects affected / exposed	28 / 248 (11.29%)	13 / 171 (7.60%)	2 / 68 (2.94%)
occurrences (all)	32	17	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	46 / 248 (18.55%)	9 / 171 (5.26%)	22 / 68 (32.35%)
occurrences (all)	66	11	76
Muscular weakness			
subjects affected / exposed	8 / 248 (3.23%)	3 / 171 (1.75%)	4 / 68 (5.88%)
occurrences (all)	8	3	5
Back pain			
subjects affected / exposed	21 / 248 (8.47%)	15 / 171 (8.77%)	3 / 68 (4.41%)
occurrences (all)	22	17	7
Myalgia			
subjects affected / exposed	32 / 248 (12.90%)	4 / 171 (2.34%)	17 / 68 (25.00%)
occurrences (all)	62	5	56
Pain in extremity			
subjects affected / exposed	21 / 248 (8.47%)	12 / 171 (7.02%)	8 / 68 (11.76%)
occurrences (all)	29	12	15
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	22 / 248 (8.87%)	9 / 171 (5.26%)	3 / 68 (4.41%)
occurrences (all)	31	9	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	82 / 248 (33.06%)	45 / 171 (26.32%)	12 / 68 (17.65%)
occurrences (all)	104	49	16
Dehydration			
subjects affected / exposed	14 / 248 (5.65%)	8 / 171 (4.68%)	0 / 68 (0.00%)
occurrences (all)	19	12	0
Hypokalaemia			
subjects affected / exposed	15 / 248 (6.05%)	14 / 171 (8.19%)	2 / 68 (2.94%)
occurrences (all)	15	17	2
Hypomagnesaemia			
subjects affected / exposed	13 / 248 (5.24%)	7 / 171 (4.09%)	0 / 68 (0.00%)
occurrences (all)	19	8	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2009	The primary purpose of this amendment was to include additional cardiac function monitoring for subjects receiving doxorubicin to be in alignment with cardiac monitoring guidelines.
05 January 2010	The main purpose of this amendment was to change the dataset for the primary objective of progression-free survival to all randomised subjects, rather than the subset of subjects with measurable disease, to reflect the intent-to-treat population, in response to scientific advice obtained from the European Medicines Agency Committee for Medicinal Products for Human Use.
15 June 2010	The main purpose of this amendment was to further clarify eligibility with regard to prior chemotherapy. Subjects were eligible if they meet either criterion: Receipt of 1 prior chemotherapy regimen that included a platinum agent regardless of setting (adjuvant, neoadjuvant, metastatic, recurrent) or disease stage, or receipt of 2 prior chemotherapy regimens, with at least 1 regimen including a platinum agent, if 1 regimen was given for stage I or II disease.
01 October 2010	The main purpose of this amendment was to fully align the protocol with recommendations of the regulatory health authorities [US Food and Drug Administration and European Medicines Agency Committee for Medicinal Products for Human Use]. The primary endpoint of progression free survival was amended to overall survival.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was terminated as per recommendation of Data Monitoring Committee as results from an interim analysis showed no favorable benefit/risk ratio for subjects and ixabepilone did not improve survival compared with control chemotherapies.

Notes: