Clinical trial results:
A Phase II, Double-Blind, Randomised, Placebo-Controlled Study to Assess the Efficacy of AZD6244 (Hyd-Sulfate) in Combination with Docetaxel, Compared with Docetaxel Alone, in 2nd Line Patients with KRAS Mutation-Positive Locally Advanced or Metastatic Non-Small Cell Lung Cancer (Stage IIIB–IV)

Summary

EudraCT number	2008-006323-31
Trial protocol	HU CZ DK ES BE FR IT BG
Global end of trial date	22 September 2011

Results information

Result version number	v1 (current)
This version publication date	09 August 2018
First version publication date	09 August 2018

Trial information

Trial identification

Sponsor protocol code	D1532C00016

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Da Vinci Building, Melbourn Science Park, Melbourn, United Kingdom, SG8 6EE
Public contact	Tracy Cunningham, AstraZeneca, +1 877-400-4656, clinicaltrialtransparency@astrazeneca.com
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 March 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2011
Global end of trial reached?	Yes
Global end of trial date	22 September 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy in terms of overall survival (OS) of AZD6244 in combination with docetaxel, compared with docetaxel alone, in second-line patients with KRAS mutation-positive locally advanced or metastatic NSCLC.

Protection of trial subjects:

1. Female and male patients were required to use reliable methods of contraception for the duration of the study as specified in the Protocol.

2. AZD6244 or placebo was to be taken on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing).

3.. During the period of treatment, patients were to avoid excessive sun exposure and use adequate sunscreen protection if sun exposure was anticipated.

4. During the study patients could receive palliative radiotherapy at the site of bone metastases that were present at baseline at the investigator's discretion.

5. No other anti-cancer agents or investigational drugs could be administered whilst patients were receiving study medication.

6. Patients who were taking coumarin anticoagulants were to have increased the frequency of assessment of anticoagulation.

7. Patients were not to take Vitamin E supplements or multivitamin supplements which provided a total daily dose in excess of 100% of the recommended daily dose of Vitamin E.

8. Throughout the study, patients were to avoid changes to, or the addition of, all concomitant medications, in particular any that could have affected the metabolism of AZD6244 (eg, CYP1A2 or 3A4 inhibitors/inducers), unless considered clinically indicated.

Background therapy:

AZD6244 (150 mg/day) in combination with docetaxel (iv 75 mg/m2 per cycle) shows improved efficacy compared to docetaxel alone in a placebo-controlled study for 2nd line patients with KRAS mutation positive locally advanced or metastatic NSCLC.

The pharmacological effects of AZD6244 have been studied extensively by examining the anti-tumour activity of AZD6244 in different in vivo and in vitro tumour models. Overall AZD6244 had strong anti-tumour activity in multiple non-clinical models, including human melanomas (LOX and A375v), human breast carcinomas (Zr-75-1 and MDA-MB-231), human pancreatic tumours (BxPC3, AsPC1, HPAC, MIA PaCa-2 and PANC 1), human lung cancer tumours (A549) and human colon carcinomas (HT-29, Colon 26 tumours, Colo205, SW620, Lovo and HCT116).

AZD6244 has demonstrated potent inhibition of BRAF or KRAS positive cell line viability and inhibition of xenograft growth both as monotherapy and in combination with a number of cytotoxic and targeted agents. Amongst the combinations with standard cytotoxic drugs, the most striking effects were seen with AZD6244 and taxotere (Haass et al 2008), temozolomide or irinotecan. In 3 xenograft models of a KRAS positive tumour (SW620 colorectal cancer, HCT-116 colorectal cancer and A549a NSCLC) a beneficial effect of the combination with

docetaxel was observed in each experiment when compared with either AZD6244 or docetaxel as monotherapy.

Evidence for comparator:

Docetaxel (TAXOTERE™, Sanofi-Aventis) is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of platinum-based chemotherapy. At a dose of 75 mg/m2, docetaxel had a significant beneficial effect on OS compared with best supportive care, and a significantly higher 1 year survival compared to the control arm of vinorelbine or ifosfamide (Shepherd et al 2000, Fossella et al 2000). Expected toxicities include hypersensitivity reactions, neutropenia, peripheral neuropathy, and fluid retention.

Actual start date of recruitment	20 April 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Brazil: 16
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Peru: 1
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	87
EEA total number of subjects	51

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)	69
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twelve countries and 67 centres were involved in the study. 422 patients screened and 87 patients randomised (44 patients to receive AZD6244 75 mg bd + docetaxel 75 mg/m2 and 43 patients to receive placebo + docetaxel 75mg/m2). One patient was randomized to the placebo group but did not receive placebo and was excluded from the safety analysis.

Pre-assignment

Screening details:

Screening procedures included; confirmation of KRAS mutation status, collection of serum and plasma samples, and patient demographic characteristics. Patient demographic characteristic assessments were conducted within 14 days prior to randomization.

Of the 422 patients screened, 87 patients were randomised.

Period 1

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

Blinding implementation details:

1. The active and placebo capsules appeared identical

2. Medication was labelled using a unique material pack code which was linked to the randomisation scheme.

3. IVRS/IWRS allocated randomisation numbers sequentially when sites called IVRS/IWRS to randomise an eligible patient.

4. IVRS/IWRS allocated the medication pack code to be dispensed to the patient

Arms

Are arms mutually exclusive?	Yes
Arm title	AZD6244 mg BD + Docetaxel

Arm description:

AZD6244 in Combination with Docetaxel

Arm type	Experimental
Investigational medicinal product name	AZD6244 (Hyd-Sulfate)
Investigational medicinal product code	
Other name	Selumetinib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Hyd-Sulfate formulation capsules with dose 75 mg twice daily

Arm title	Docetaxel Alone

Arm description:

Placebo + Docetaxel

Arm type	Active comparator
Investigational medicinal product name	Docetaxel Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection/infusion
Routes of administration	Intramuscular and intravenous use

Dosage and administration details:

20 mg and 80 mg

Number of subjects in period 1	AZD6244 mg BD + Docetaxel	Docetaxel Alone
Started	44	43
Completed	44	43

Baseline characteristics

Reporting groups	
Reporting group title	AZD6244 mg BD + Docetaxel
Reporting group description: AZD6244 in Combination with Docetaxel	
Reporting group title	Docetaxel Alone
Reporting group description: Placebo + Docetaxel	

Reporting group values	AZD6244 mg BD + Docetaxel	Docetaxel Alone	Total
Number of subjects	44	43	87
Age Categorical			
ITT analysis set			
Units: Subjects			
<= 55 years	15	15	30
> 55 years	29	28	57
Age Continuous			
ITT analysis set			
Units: years			
median	59.5	59.0	
full range (min-max)	26 to 79	37 to 76	-
Gender Categorical			
ITT analysis set			
Units: Subjects			
Female	23	23	46
Male	21	20	41
Race			
ITT analysis set			
Units: Subjects			
White	41	40	81
Black or African American	1	1	2
Other	2	2	4
Ethnic Group			
ITT analysis set			
Units: Subjects			
Hispanic or Latino	7	10	17
Not Applicable	37	33	70
WHO Performance Status			
ITT analysis set			
Units: Subjects			
(0) Normal activity	21	21	42
(1) Restricted activity	23	22	45
Histology type			
ITT analysis set			
Units: Subjects			
Squamous carcinoma	3	6	9
Adenocarcinoma	30	23	53

Adenocarcinoma: Bronchoalveolar	6	10	16
Adenosquamous carcinoma	2	1	3
Large cell carcinoma (NOS)	2	0	2
Other	1	3	4
AJCC stage classification			
ITT analysis set			
Units: Subjects			
M0 (No distant metastasis)	5	1	6
M1 (Distant metastasis present)	39	42	81
Height			
ITT analysis set			
Units: cm			
arithmetic mean	166.1	165.5	
standard deviation	± 9.24	± 9.59	-
Weight			
ITT analysis set			
Units: kg			
arithmetic mean	68.6	69.3	
standard deviation	± 18.57	± 16.41	-

End points

End points reporting groups

Reporting group title	AZD6244 mg BD + Docetaxel
Reporting group description: AZD6244 in Combination with Docetaxel	
Reporting group title	Docetaxel Alone
Reporting group description: Placebo + Docetaxel	

Primary: Overall survival, MITT

End point title	Overall survival, MITT

End point description:

OS was calculated as the interval from the date of randomisation to the date of patient death (any cause). Patients who had not died at the time of the final analysis, or who withdrew consent, were censored at the last date the patient was known to be alive. The MITT analysis set was a subset of the ITT population including only patients without important detected protocol deviations. The end of this study was defined as the date when all patients receiving AZD6244 had been followed for a minimum period of 12 months since start of treatment, or the date of the final analysis of the data, whichever was later.

End point type	Primary

End point timeframe:

All patients were followed until death, withdrawal of consent, or the end of the study.

End point values	AZD6244 mg BD + Docetaxel	Docetaxel Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: Count				
Number who died	29	27		
Number who were alive as of DCO	13	13		
Number withdrawn consent	1	0		

Statistical analyses

Statistical analysis title	Overall survival (MITT analysis set)

Statistical analysis description:

The analysis was performed using Cox proportional hazards model; The model allows for the effect of treatment and included terms for WHO PS, gender, histology and smoking status.

Comparison groups	AZD6244 mg BD + Docetaxel v Docetaxel Alone

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.2069 [2]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.8
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.56
upper limit	1.14

Notes:

[1] - A Hazard Ratio less than 1 favoured AZD6244 + Docetaxel.

[2] - One-sided p-value

Secondary: Progression-free survival, MITT

End point title	Progression-free survival, MITT

End point description:

PFS was defined as the interval between the date of randomisation and the earlier date of objective disease progression per RECIST criteria or death due to any cause in the absence of progression. Patients who did not progress or die at the time of analysis were censored at the time of their latest evaluable objective tumour assessment. This also included patients who withdrew consent. The MITT analysis set was a subset of the ITT population including only patients without important detected protocol deviations. RECIST measurements were used to derive the secondary variables of PFS.

End point type	Secondary

End point timeframe:

Time until objective disease progression or DCO for the analysis of PFS.

End point values	AZD6244 mg BD + Docetaxel	Docetaxel Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: Count				
Progression: Total	35	36		
Progression: RECIST progression	28	27		
Progression: Death	7	9		
Progression > 2 assessments: Total	1	2		
Progression > 2 assessments: Progression	0	1		
Progression > 2 assessments: Death	1	1		
No progression: Total	7	2		
Alive and Progression Free at the time of DCO	6	2		
No progression: Subject Voluntary discontinuation	1	0		

Statistical analyses

Statistical analysis title	Progression-free survival (MITT analysis set)

Statistical analysis description:

The analysis was performed using a Cox proportional hazards model. The model allowed for the effect of treatment and included terms for WHO PS, gender, histology, and smoking status.

Comparison groups	AZD6244 mg BD + Docetaxel v Docetaxel Alone
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0138 [4]
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	0.58
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.42
upper limit	0.79

Notes:

[3] - A Hazard Ratio (HR) < 1 favoured AZD6244 + Docetaxel.

[4] - One-sided p-value

Secondary: Objective Response Rate, MITT

End point title	Objective Response Rate, MITT

End point description:

Overall response rate (ORR) is defined as the proportion of patients who have a best response of either CR or PR. RECIST measurements were used to derive the secondary variables of ORR.

End point type	Secondary

End point timeframe:

Time until objective disease progression or DCO for the analysis of PFS.

End point values	AZD6244 mg BD + Docetaxel	Docetaxel Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40		
Units: Count				
Response: Total	16	0		
Complete Response: Total	0	0		
Complete Response: Confirmed	0	0		
Complete Response: Unconfirmed	0	0		
Partial Response: Total	16	0		
Partial Response: Confirmed	11	0		
Partial Response: Unconfirmed	5	0		
Non-Response: Total	27	40		
Non-Response: Stable Disease >= 6 Weeks	19	20		
Non-Response: Progression (All)	8	18		
Non-Response: RECIST Progression	6	13		
Non-Response: Early Death	2	5		
Non-Response: Not Evaluable	0	2		

Non-Response: Stable Disease < 6 Weeks	0	0		
No valid or evaluable baseline assessment	0	0		
No evaluable follow-up assessment	0	2		

Statistical analyses

Statistical analysis title	Objective Response Rate
Comparison groups	AZD6244 mg BD + Docetaxel v Docetaxel Alone
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [5]
Method	Fisher exact
Parameter estimate	Fisher exact test

Notes:

[5] - 2 - sided mid p-value

Secondary: Duration of Response, MITT

End point title	Duration of Response, MITT

End point description:

Duration of response is defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The MITT analysis set was a subset of the ITT population including only patients without important detected protocol deviations.

End point type	Secondary

End point timeframe:

From randomization till progression, death or study discontinuation

End point values	AZD6244 mg BD + Docetaxel	Docetaxel Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	40[6]		
Units: Days				
arithmetic mean (standard error)				
Mean Duration of Response (Days)	193.4 (± 0.207)	00 (± 00)		

Notes:

[6] - No subjects in the Docetaxel alone arm had a RECIST response

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from baseline in tumour size at week 6, MITT

End point title	Percentage change from baseline in tumour size at week 6, MITT

End point description:

Tumour size (TS) is the sum of longest diameters of target lesions.

% change from baseline=[(week 6 TS/baseline TS)-1]*100

End point type	Secondary

End point timeframe:

At week 6

End point values	AZD6244 mg BD + Docetaxel	Docetaxel Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	38		
Units: Percentage change				
least squares mean (confidence interval 80%)				
Percentage change in tumour size at Week 6	-16.98 (-27.1 to -6.85)	0.05 (-9.84 to 9.93)		

Statistical analyses

Statistical analysis title	Change in tumour size at Week 6

Statistical analysis description:

LS means were adjusted for baseline tumour size, time from baseline scan to randomisation, WHO PS, gender, histology, and smoking status. LS means were also weighted in line with the prevalence of the primary covariates.

Comparison groups	AZD6244 mg BD + Docetaxel v Docetaxel Alone
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	LSMeans difference
Point estimate	-17.03
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-25.2
upper limit	-8.86

Secondary: Percentage change from baseline in tumour size at Week 12, MITT

End point title	Percentage change from baseline in tumour size at Week 12, MITT

End point description:

Tumour size (TS) is the sum of longest diameters of target lesions.

% change from baseline=[(week 12 TS/baseline TS)-1]*100

End point type	Secondary

End point timeframe:

At week 12

End point values	AZD6244 mg BD + Docetaxel	Docetaxel Alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	38		
Units: Percentage				
least squares mean (confidence interval 80%)				
Percentage change in tumour size at Week 12	-19.38 (-34.7 to -4.09)	6.62 (-8.31 to 21.54)		

Statistical analyses

Statistical analysis title	Change from baseline in tumour size at Week 12

Statistical analysis description:

LS means were adjusted for baseline tumour size, time from baseline scan to randomisation, WHO PS, gender, histology, and smoking status. LS means were also weighted in line with the prevalence of the primary covariates.

Comparison groups	AZD6244 mg BD + Docetaxel v Docetaxel Alone
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	ANCOVA
Parameter estimate	LSMeans difference
Point estimate	-26
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-38.34
upper limit	-13.7

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug until last study visit	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14

Reporting groups	
Reporting group title	Placebo + Docetaxel
Reporting group description: -	
Reporting group title	AZD6244 75 mg BD + Docetaxel
Reporting group description: -	

Serious adverse events	Placebo + Docetaxel	AZD6244 75 mg BD + Docetaxel	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 42 (30.95%)	26 / 44 (59.09%)	
number of deaths (all causes)	28	30	
number of deaths resulting from adverse events	3	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR NECROSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
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			
FACE OEDEMA			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPNOEA EXERTIONAL			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTERSTITIAL LUNG DISEASE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
PNEUMOTHORAX			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY HAEMORRHAGE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 3	
Investigations			
BLOOD CREATINE PHOSPHOKINASE INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CREATININE RENAL CLEARANCE DECREASED			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROCARDIOGRAM T WAVE INVERSION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ACUTE CORONARY SYNDROME			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FLUTTER			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC ARREST			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
PERICARDIAL EFFUSION			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SINUS BRADYCARDIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
SYNCOPE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	6 / 44 (13.64%)	
occurrences causally related to treatment / all	0 / 0	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	3 / 42 (7.14%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	0 / 3	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPEPSIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC ULCER HAEMORRHAGE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETROPERITONEAL HAEMATOMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DERMATITIS ACNEIFORM			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSORIASIS			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
BACK PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN IN EXTREMITY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (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			
CYSTITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMPYEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION BACTERIAL			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
NEUTROPENIC INFECTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	4 / 44 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
RESPIRATORY TRACT INFECTION VIRAL			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Docetaxel	AZD6244 75 mg BD + Docetaxel	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 42 (97.62%)	43 / 44 (97.73%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT PLEURAL EFFUSION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	3	
TUMOUR PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
FLUSHING			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	3 / 42 (7.14%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
HAEMATOMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
HYPERAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HYPERTENSION			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	2 / 42 (4.76%)	4 / 44 (9.09%)	
occurrences (all)	2	4	
HYPERTENSIVE CRISIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HYPOTENSION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	4 / 44 (9.09%)	
occurrences (all)	1	5	
LYMPHOEDEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	5	
ORTHOSTATIC HYPOTENSION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PHLEBITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	4	0	
THROMBOPHLEBITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
THROMBOSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	11 / 42 (26.19%)	14 / 44 (31.82%)	
occurrences (all)	12	26	
CATHETER SITE PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
CHEST PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)	
occurrences (all)	2	1	
CHILLS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
EARLY SATIETY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
FACE OEDEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
FATIGUE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	14 / 42 (33.33%)	12 / 44 (27.27%)	
occurrences (all)	15	15	
GENERALISED OEDEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
INFLUENZA LIKE ILLNESS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	

LOCALISED OEDEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
MUCOSAL INFLAMMATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
NON-CARDIAC CHEST PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
OEDEMA PERIPHERAL			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	7 / 42 (16.67%)	18 / 44 (40.91%)	
occurrences (all)	8	22	
PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
PYREXIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	5 / 42 (11.90%)	12 / 44 (27.27%)	
occurrences (all)	5	13	
Immune system disorders			
DRUG HYPERSENSITIVITY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
PELVIC PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
VAGINAL LESION			

alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
COUGH			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	8 / 42 (19.05%)	10 / 44 (22.73%)	
occurrences (all)	8	10	
DYSPHONIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	4	
DYSPNOEA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	9 / 42 (21.43%)	5 / 44 (11.36%)	
occurrences (all)	10	5	
DYSPNOEA EXERTIONAL			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	10 / 42 (23.81%)	7 / 44 (15.91%)	
occurrences (all)	10	7	
EPISTAXIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	7 / 44 (15.91%)	
occurrences (all)	2	8	
HAEMOPTYSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	4 / 44 (9.09%)	
occurrences (all)	2	4	
HICCUPS			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)		
occurrences (all)	0	2		
INTERSTITIAL LUNG DISEASE				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)		
occurrences (all)	0	1		
NASAL CONGESTION				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	2 / 42 (4.76%)	3 / 44 (6.82%)		
occurrences (all)	2	3		
OROPHARYNGEAL PAIN				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)		
occurrences (all)	1	2		
ORTHOPNOEA				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)		
occurrences (all)	1	0		
PLEURAL EFFUSION				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)		
occurrences (all)	1	2		
PRODUCTIVE COUGH				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)		
occurrences (all)	2	1		
PULMONARY CONGESTION				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)		
occurrences (all)	1	0		
PULMONARY EMBOLISM				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)		
occurrences (all)	1	0		

PULMONARY HYPERTENSION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
RALES			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
RHINITIS ALLERGIC			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
RHINORRHOEA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
SINUS CONGESTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
WHEEZING			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	2	
Psychiatric disorders			
ANXIETY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	3 / 42 (7.14%)	4 / 44 (9.09%)	
occurrences (all)	3	4	
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
DEPRESSION			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
INSOMNIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	4 / 42 (9.52%)	2 / 44 (4.55%)	
occurrences (all)	4	2	
MOOD ALTERED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
PANIC ATTACK			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
ALBUMIN URINE PRESENT			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
BLOOD ALKALINE PHOSPHATASE INCREASED			
alternative dictionary used:			

MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	3	
BLOOD CREATININE INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
BLOOD GLUCOSE INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
BLOOD PRESSURE INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	4 / 44 (9.09%)	
occurrences (all)	1	8	
BREATH SOUNDS ABNORMAL			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	2	
C-REACTIVE PROTEIN INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
EJECTION FRACTION DECREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	2	
ELECTROCARDIOGRAM QT PROLONGED			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
HAEMOGLOBIN DECREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	3 / 44 (6.82%)	
occurrences (all)	1	4	
WEIGHT DECREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	2	
WEIGHT INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
WHITE BLOOD CELL COUNT DECREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
WHITE BLOOD CELL COUNT INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
CONTUSION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)	
occurrences (all)	2	1	
EXCORIATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
FRACTURED ISCHIUM			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PROCEDURAL PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
RADIATION PNEUMONITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
RADIATION SKIN INJURY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
ARRHYTHMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
DIASTOLIC DYSFUNCTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
HYPERTENSIVE HEART DISEASE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
LEFT VENTRICULAR DYSFUNCTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
PALPITATIONS			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
PERICARDIAL EFFUSION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
SINUS BRADYCARDIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
SINUS TACHYCARDIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
TACHYCARDIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)	
occurrences (all)	1	2	
TRICUSPID VALVE INCOMPETENCE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
AGEUSIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
BALANCE DISORDER			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
CEREBELLAR ATAXIA			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)		
occurrences (all)	0	1		
DIZZINESS				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	3 / 42 (7.14%)	4 / 44 (9.09%)		
occurrences (all)	3	5		
DIZZINESS POSTURAL				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)		
occurrences (all)	1	0		
DYSGEUSIA				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	2 / 42 (4.76%)	5 / 44 (11.36%)		
occurrences (all)	2	6		
HEADACHE				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	5 / 42 (11.90%)	6 / 44 (13.64%)		
occurrences (all)	5	8		
LETHARGY				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)		
occurrences (all)	0	1		
MEMORY IMPAIRMENT				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)		
occurrences (all)	1	0		
NEUROPATHY PERIPHERAL				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	5 / 44 (11.36%)		
occurrences (all)	1	5		
PARAESTHESIA				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	2 / 42 (4.76%)	3 / 44 (6.82%)		
occurrences (all)	3	7		

PARESIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	3	
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)	
occurrences (all)	2	1	
SCIATICA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
SOMNOLENCE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
SYNCOPE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	3	
TREMOR			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	5 / 42 (11.90%)	7 / 44 (15.91%)	
occurrences (all)	6	7	
ANAEMIA OF MALIGNANT DISEASE			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HAEMORRHAGIC ANAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
LEUKOCYTOSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)	
occurrences (all)	2	3	
LEUKOPENIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	4 / 42 (9.52%)	3 / 44 (6.82%)	
occurrences (all)	5	5	
NEUTROPENIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	13 / 42 (30.95%)	16 / 44 (36.36%)	
occurrences (all)	19	17	
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)	
occurrences (all)	2	1	
Ear and labyrinth disorders			
HYPOACUSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
OTORRHOEA			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
TINNITUS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
VERTIGO			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Eye disorders			
BLEPHARITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
CATARACT			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	0 / 44 (0.00%)	
occurrences (all)	2	0	
CONJUNCTIVAL HYPERAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
CONJUNCTIVAL OEDEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
CONJUNCTIVITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	3 / 44 (6.82%)	
occurrences (all)	1	3	
DIABETIC RETINOPATHY			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
DIPLOPIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
DRY EYE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
EYE IRRITATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
EYELID OEDEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)	
occurrences (all)	1	2	
LACRIMATION INCREASED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	3 / 42 (7.14%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
PERIORBITAL OEDEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	4 / 44 (9.09%)	
occurrences (all)	1	10	
PHOTOPSIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
VISION BLURRED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	6 / 44 (13.64%)	
occurrences (all)	1	7	

VISUAL ACUITY REDUCED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
ABDOMINAL DISCOMFORT			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	8 / 44 (18.18%)	
occurrences (all)	1	8	
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	4 / 42 (9.52%)	8 / 44 (18.18%)	
occurrences (all)	4	9	
ANAL SPHINCTER ATONY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
APHTHOUS STOMATITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
CHEILITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
CONSTIPATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	8 / 42 (19.05%)	14 / 44 (31.82%)	
occurrences (all)	10	20	
DIARRHOEA			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	7 / 42 (16.67%)	32 / 44 (72.73%)	
occurrences (all)	8	60	
DRY MOUTH			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	3 / 44 (6.82%)	
occurrences (all)	1	4	
DYSPEPSIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	4 / 42 (9.52%)	8 / 44 (18.18%)	
occurrences (all)	4	10	
DYSPHAGIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
FAECAL INCONTINENCE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
GASTRITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
GASTROOESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
GINGIVAL BLEEDING			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
GINGIVAL SWELLING			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	

HAEMORRHOIDAL HAEMORRHAGE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HAEMORRHOIDS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HYPERCHLORHYDRIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
LIP DRY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
LIP SWELLING			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
NAUSEA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	12 / 42 (28.57%)	19 / 44 (43.18%)	
occurrences (all)	20	32	
ODYNOPHAGIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
PEPTIC ULCER			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
RECTAL HAEMORRHAGE			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
STOMATITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	8 / 42 (19.05%)	16 / 44 (36.36%)	
occurrences (all)	8	25	
VOMITING			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	9 / 42 (21.43%)	18 / 44 (40.91%)	
occurrences (all)	12	28	
Hepatobiliary disorders			
CHOLELITHIASIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
ACNE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)	
occurrences (all)	1	3	
ALOPECIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	9 / 42 (21.43%)	13 / 44 (29.55%)	
occurrences (all)	9	13	
BLISTER			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
DERMATITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
DERMATITIS ACNEIFORM			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	2 / 42 (4.76%)	16 / 44 (36.36%)	
occurrences (all)	2	18	
DRY SKIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	4 / 42 (9.52%)	10 / 44 (22.73%)	
occurrences (all)	4	12	
ECCHYMOSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
ERYTHEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	4 / 44 (9.09%)	
occurrences (all)	0	4	
HYPERHIDROSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
INGROWING NAIL			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
MADAROSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
NAIL DISCOLOURATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	4 / 44 (9.09%)	
occurrences (all)	0	4	
NAIL DISORDER			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	

NIGHT SWEATS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
ONYCHOLYSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
PAIN OF SKIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
PALMAR ERYTHEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PETECHIAE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PRURITUS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	3 / 44 (6.82%)	
occurrences (all)	1	3	
RASH ERYTHEMATOUS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	3 / 44 (6.82%)	
occurrences (all)	1	4	
RASH MACULAR			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	8	
RASH MACULO-PAPULAR			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
RASH PRURITIC			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
SCAR PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
SKIN CHAPPED			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
SKIN DISCOLOURATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
SKIN EXFOLIATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	3 / 42 (7.14%)	4 / 44 (9.09%)	
occurrences (all)	3	6	
SKIN FISSURES			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
SKIN ULCER			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	2	

SUBCUTANEOUS EMPHYSEMA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
URTICARIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
Renal and urinary disorders			
DYSURIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
HAEMATURIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
LEUKOCYTURIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
MICROALBUMINURIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	2	
OLIGURIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
POLLAKIURIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
POLYURIA			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
RENAL FAILURE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
RENAL FAILURE ACUTE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
URINARY HESITATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
URINARY INCONTINENCE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
URINARY RETENTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	8 / 42 (19.05%)	2 / 44 (4.55%)	
occurrences (all)	13	2	
BACK PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	4 / 42 (9.52%)	2 / 44 (4.55%)	
occurrences (all)	4	2	
BONE PAIN			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
CHEST WALL MASS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
MUSCLE CONTRACTURE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
MUSCLE SPASMS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
MUSCULAR WEAKNESS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	
MUSCULOSKELETAL CHEST PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	8 / 42 (19.05%)	3 / 44 (6.82%)	
occurrences (all)	10	3	
MUSCULOSKELETAL PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	2	
MYALGIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	7 / 42 (16.67%)	6 / 44 (13.64%)	
occurrences (all)	8	7	
NECK PAIN			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	2	

OSTEOARTHRITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PAIN IN EXTREMITY			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)	
occurrences (all)	1	2	
SENSATION OF HEAVINESS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
Infections and infestations			
BACTERAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
BRONCHITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	2 / 44 (4.55%)	
occurrences (all)	2	3	
CANDIDIASIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
CYSTITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
EAR INFECTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
ERYSIPELAS			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)		
occurrences (all)	0	1		
FOLLICULITIS				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)		
occurrences (all)	0	2		
GASTROENTERITIS				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)		
occurrences (all)	1	0		
HERPES ZOSTER				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)		
occurrences (all)	1	0		
INFLUENZA				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)		
occurrences (all)	2	1		
LUNG INFECTION				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)		
occurrences (all)	1	1		
MASTITIS				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)		
occurrences (all)	0	1		
MORAXELLA INFECTION				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)		
occurrences (all)	0	1		
NASOPHARYNGITIS				
alternative dictionary used: MedDRA 14				
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)		
occurrences (all)	2	1		

ONYCHOMYCOSIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
ORAL CANDIDIASIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	4 / 44 (9.09%)	
occurrences (all)	0	4	
OTITIS MEDIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PARONYCHIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
PHARYNGITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PHARYNGITIS STREPTOCOCCAL			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
PNEUMONIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)	
occurrences (all)	2	1	
RASH PUSTULAR			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	3 / 44 (6.82%)	
occurrences (all)	0	3	
RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
RHINITIS			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	1 / 44 (2.27%)	
occurrences (all)	1	1	
SKIN CANDIDA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	0 / 44 (0.00%)	
occurrences (all)	1	0	
SKIN INFECTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
UPPER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	3 / 42 (7.14%)	2 / 44 (4.55%)	
occurrences (all)	3	2	
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	10 / 42 (23.81%)	15 / 44 (34.09%)	
occurrences (all)	13	19	
DEHYDRATION			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	5 / 44 (11.36%)	
occurrences (all)	2	6	
HYPERCHOLESTEROLAEMIA			
alternative dictionary used: MedDRA 14			

subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HYPERGLYCAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	3 / 42 (7.14%)	4 / 44 (9.09%)	
occurrences (all)	4	4	
HYPERKALAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HYPERPHOSPHATAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HYPERTRIGLYCERIDAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HYPOALBUMINAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	2 / 42 (4.76%)	1 / 44 (2.27%)	
occurrences (all)	3	1	
HYPOCALCAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
HYPOKALAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	2 / 44 (4.55%)	
occurrences (all)	0	2	
HYPOMAGNESAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	

HYPONATRAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	1 / 42 (2.38%)	2 / 44 (4.55%)	
occurrences (all)	1	2	
HYPOVOLAEMIA			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	
INCREASED APPETITE			
alternative dictionary used: MedDRA 14			
subjects affected / exposed	0 / 42 (0.00%)	1 / 44 (2.27%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2009	Correction of an error in the protocol. AZD6244/placebo should be taken on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing), as described in Section 6.4.2.
21 October 2009	Clarification that consent for the optional use of residual samples for other biomarkers research is in a separate biological samples research addendum to the mutation status screening informed consent. There are other corrections to the protocol.
02 February 2010	To clarify that any methodology used by local laboratories to determine KRAS mutation status is acceptable, as long as the methodology has been assessed and approved by AstraZeneca. To allow the use of accredited commercial laboratories such as Genzyme or Lab 21 to confirm KRAS mutation status.
01 November 2010	Part way through the recruitment period, Bulgaria were brought on board to participate in the study to aid with recruitment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported