Clinical trial results:
A Phase III, International, Randomised, Double-Blind, Parallel-Group, Multi-Centre Study to Assess the Efficacy of ZD6474(ZACTIMA™) Plus Best Supportive Care Versus Placebo Plus Best Supportive Care in Patients With Locally Advanced or Metastatic (Stage IIIB – IV) Non-Small Cell Lung Cancer (NSCLC) after Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor (EGFR TKI)

Summary

EudraCT number	2006-002384-12
Trial protocol	BE DE FR AT NL GB IT ES
Global end of trial date	30 November 2014

Results information

Result version number	v1 (current)
This version publication date	09 June 2016
First version publication date	09 June 2016

Trial information

Trial identification

Sponsor protocol code	D4200C00044

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00404924
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Gabriella Mariani, AstraZeneca, aztrial_results_posting@astrazeneca.com
Scientific contact	Gabriella Mariani, AstraZeneca, aztrial_results_posting@astrazeneca.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	30 March 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2009
Global end of trial reached?	Yes
Global end of trial date	30 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to demonstrate an improvement in overall survival for ZD6474 plus best supportive care (BSC) compared with placebo plus BSC in patients with locally advanced or metastatic NSCLC after prior therapy with an EGFR TKI.

Protection of trial subjects:

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	15 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 26
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Austria: 17
Country: Number of subjects enrolled	Belgium: 44
Country: Number of subjects enrolled	Canada: 73
Country: Number of subjects enrolled	China: 170
Country: Number of subjects enrolled	France: 61
Country: Number of subjects enrolled	Germany: 112
Country: Number of subjects enrolled	Hong Kong: 44
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 62
Country: Number of subjects enrolled	Korea, Republic of: 220
Country: Number of subjects enrolled	Mexico: 23
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Peru: 13
Country: Number of subjects enrolled	Philippines: 9
Country: Number of subjects enrolled	Singapore: 16

Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Taiwan: 135
Country: Number of subjects enrolled	Thailand: 33
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	1140
EEA total number of subjects	341

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)	700
From 65 to 84 years	434
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

First patient enrolled 08 November 2006, last patient enrolled 09 October 2008, cut off date 19 October 2009. 1140 patients were screened in the study.

Pre-assignment

Screening details:

1140 patients signed inform consent and 924 randomised

Pre-assignment period milestones

Number of subjects started	1140
Number of subjects completed	924

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, serious fatal: 4
Reason: Number of subjects	Consent withdrawn by subject: 12
Reason: Number of subjects	Protocol deviation: 200

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Vandetanib 300 mg

Arm description:

vandetanib (300 mg daily) plus best supportive care

Arm type	Experimental
Investigational medicinal product name	ZACTIMA
Investigational medicinal product code	ZD6474
Other name	Caprelsa
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single oral dose 300mg daily

Arm title	Placebo

Arm description:

Placebo plus best supportive care

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:
Single oral dose 300mg daily

Number of subjects in period 1[1]	Vandetanib 300 mg	Placebo
Started	617	307
Completed	14	1
Not completed	603	306
Consent withdrawn by subject	26	13
Adverse event, non-fatal	75	16
Condition under investigation worsened	475	264
Not Specified	25	11
Lost to follow-up	1	1
Randomised but not received treatment	1	1

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: I have an error stating that the number for the worldwide enrolled is not equal to the number of patients who started the overall study at baseline - if the number enrolled is the number screened then this won't equal the number at baseline as this is the number randomised

Baseline characteristics

Reporting groups	
Reporting group title	Vandetanib 300 mg
Reporting group description: vandetanib (300 mg daily) plus best supportive care	
Reporting group title	Placebo
Reporting group description: Placebo plus best supportive care	

Reporting group values	Vandetanib 300 mg	Placebo	Total
Number of subjects	617	307	924
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	396	180	576
From 65-74 years	157	92	249
75 years and over	64	35	99
Age Continuous | Units: years			
arithmetic mean	59.8	60.6	
full range (min-max)	20 to 85	21 to 84	-
Gender, Male/Female Units: Participants			
Female	329	160	489
Male	288	147	435

End points

End points reporting groups	
Reporting group title	Vandetanib 300 mg
Reporting group description:	
vandetanib (300 mg daily) plus best supportive care	
Reporting group title	Placebo
Reporting group description:	
Placebo plus best supportive care	

Primary: Overall Survival (OS)	
End point title	Overall Survival (OS)
End point description:	
Overall Survival (OS) is defined as the time from date of randomization until death. Any blinded/unknown patient which have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive (ie, their status must be known at the censored date and should not be lost to follow up or unknown).	
End point type	Primary
End point timeframe:	
Time to death in months	

End point values	Vandetanib 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	617	307		
Units: Months				
median (confidence interval)	8.5 (7.81 to 9.76)	7.8 (6.08 to 9.17)		

Statistical analyses

Statistical analysis title	Summary of Primary Analysis of Overall Survival
Comparison groups	Vandetanib 300 mg v Placebo
Number of subjects included in analysis	924
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5273
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95.2 %
sides	2-sided
lower limit	0.81
upper limit	1.11

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Median time (in months) from randomisation until objective disease progression (determined by RECIST assessments) or death (by any cause in the absence of objective progression) provided death is within 3 months from the last evaluable RECIST assessment

End point type	Secondary

End point timeframe:

RECIST tumour assessments carried out every 8 weeks from randomisation until objective disease progression

End point values	Vandetanib 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	617	307		
Units: month				
median (confidence interval)	1.9 (1.84 to 2.23)	1.8 (1.74 to 1.84)		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The ORR is the number of patients that are responders ie those patients with a confirmed best objective response of complete response (CR) or partial response (PR) as defined by RECIST criteria. The categories for best objective response are CR, PR, stable disease (SD)>= 8 weeks, progressive disease (PD) or NE.

End point type	Secondary

End point timeframe:

Each patient was assessed for objective response from the sequence of RECIST scan data up to data cut off. RECIST tumour assessments carried out every 8 weeks from randomisation until objective disease progression.

End point values	Vandetanib 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	617	307		
Units: Participants	16	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

Disease control rate is defined as the number of patients who achieved disease control at 8 weeks following randomisation. Disease control at 8 weeks is defined as a best objective response of complete response (CR), partial response (PR) or stable disease (SD) >= 8 weeks

End point type	Secondary

End point timeframe:

RECIST tumour assessments carried out every 8 weeks from randomisation until objective disease progression

End point values	Vandetanib 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	617	307		
Units: Participants	189	48		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

Response is defined as a confirmed best objective response of CR or PR. Duration of response is defined as time from the date of first documented response until date of documented progression or death in the absence of disease progression (provided death is within 3 months of last RECIST assessment)

End point type	Secondary

End point timeframe:

RECIST tumour assessments carried out every 8 weeks from randomisation until objective disease progression

End point values	Vandetanib 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	2		
Units: Weeks				
median (confidence interval)	23.9 (16.57 to 27)	24.3 (16 to 32.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to deterioration of disease-related symptoms (TDS) by questionnaire - the lung cancer subscale (LCS) a selection of the FACT-L focusing on symptoms of lung cancer plus pain and fatigue (LCS-PF)

End point title	Time to deterioration of disease-related symptoms (TDS) by questionnaire - the lung cancer subscale (LCS) a selection of the FACT-L focusing on symptoms of lung cancer plus pain and fatigue (LCS-PF)

End point description:

Time to deterioration in symptoms is defined as the interval from the date of randomization to the first assessment of 'worsened' with no visit assessment of 'improved' within the next 28 days. Where assessment is by a selection of questions from the Functional Assessment of Cancer Therapy for Lung Cancer (FACT-L) questionnaire.

End point type	Secondary

End point timeframe:

Disease-related symptom assessments are to be administered at screening (within 7 days before the first dose of study medication) and every 4 weeks thereafter, at discontinuation of study treatment and at the 30-day follow-up visit

End point values	Vandetanib 300 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	617	307		
Units: weeks				
median (inter-quartile range (Q1-Q3))	6.1 (5.14 to 8.14)	7.1 (5.86 to 8.43)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected up to 60days after discontinuation of study treatment.

Adverse event reporting additional description:

The Safety Analysis Set included 922 patients (619 vandetanib & 303 placebo), which represents more than 99% of all randomized pts. 2 (1 in each arm) were excluded from the SAS as they were not dosed. Additionally 3 pts randomized to receive placebo received at least one dose of vandetanib, these 3 pts are included in the vandetanib arm in the SAS

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Vandetanib

Reporting group description:

Vandetanib 300 mg

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	Vandetanib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	160 / 619 (25.85%)	63 / 303 (20.79%)	
number of deaths (all causes)	474	230	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	7 / 619 (1.13%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	5 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial Thrombosis Limb			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular Vein Thrombosis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis Superficial			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visceral Arterial Ischaemia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 619 (0.81%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 619 (0.48%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Fatigue			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 619 (0.48%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 619 (0.48%)	3 / 303 (0.99%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug Hypersensitivity			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic Reaction			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	12 / 619 (1.94%)	5 / 303 (1.65%)	
occurrences causally related to treatment / all	1 / 14	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 619 (0.81%)	5 / 303 (1.65%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 619 (0.48%)	5 / 303 (1.65%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemoptysis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 619 (0.48%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	2 / 2	0 / 0	
Cough			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute Respiratory Distress Syndrome			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bronchial Haemorrhage			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bronchospasm			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Idiopathic Pulmonary Fibrosis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Artery Thrombosis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Haemorrhage			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory Failure			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory Tract Haemorrhage			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional State			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Electrocardiogram T Wave Inversion			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase Increased			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil Count Decreased			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur Fracture			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Dislocation			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Injuries			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax Traumatic			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist Fracture			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Failure			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Myocardial Infarction			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Angina Pectoris			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (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 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Valve Disease			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial Effusion			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Convulsion			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	5 / 619 (0.81%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 619 (0.00%)	3 / 303 (0.99%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 619 (0.48%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 619 (0.48%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cerebral Haemorrhage			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive Disorder			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss Of Consciousness			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial Seizures			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid Haemorrhage			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischaemic Attack			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile Neutropenia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	3 / 619 (0.48%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision Blurred			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual Acuity Reduced			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	8 / 619 (1.29%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	5 / 8	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Vomiting				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	4 / 619 (0.65%)	3 / 303 (0.99%)		
occurrences causally related to treatment / all	2 / 5	1 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Nausea				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	2 / 619 (0.32%)	1 / 303 (0.33%)		
occurrences causally related to treatment / all	2 / 2	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal Distension				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Abdominal Pain				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ascites				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				

subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Ulcer			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Perforation			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrooesophageal Reflux Disease			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Gingival Pain				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ileus Paralytic				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Intestinal Haemorrhage				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Intestinal Perforation				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 1		
Neutropenic Colitis				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia Oral			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis Intestinalis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile Duct Stenosis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytolytic Hepatitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 619 (0.65%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson Syndrome			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 619 (0.48%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Photosensitivity Reaction			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	1 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dermatitis Allergic				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Dry Skin				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Erythema				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Erythema Multiforme				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)		
occurrences causally related to treatment / all	2 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Rash Pruritic				
alternative dictionary used: MedDRA 12.1				
alternative assessment type: Systematic				

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary Retention			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Urinary			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Acute			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Incontinence			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	2 / 303 (0.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle Twitching			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	21 / 619 (3.39%)	6 / 303 (1.98%)	
occurrences causally related to treatment / all	0 / 26	0 / 7	
deaths causally related to treatment / all	0 / 3	0 / 3	
Sepsis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 619 (0.48%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung Infection			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary Tract Infection			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 619 (0.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis Bacterial			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial Sepsis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter Site Infection			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial Infection			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (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 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection Site Abscess			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar Pneumonia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower Respiratory Tract Infection			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal Sepsis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous Abscess			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	4 / 619 (0.65%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased Appetite			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 619 (0.32%)	0 / 303 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 619 (0.00%)	1 / 303 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 619 (0.16%)	0 / 303 (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	Vandetanib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	557 / 619 (89.98%)	234 / 303 (77.23%)	
Investigations			
Weight Decreased			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	47 / 619 (7.59%)	18 / 303 (5.94%)	
occurrences (all)	49	18	
Electrocardiogram Qt Prolonged			

alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	37 / 619 (5.98%) 48	1 / 303 (0.33%) 1	
Vascular disorders Hypertension alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	160 / 619 (25.85%) 182	9 / 303 (2.97%) 9	
Nervous system disorders Dizziness alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	68 / 619 (10.99%) 79	27 / 303 (8.91%) 28	
Headache alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	61 / 619 (9.85%) 70	24 / 303 (7.92%) 25	
Blood and lymphatic system disorders Anaemia alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	19 / 619 (3.07%) 22	19 / 303 (6.27%) 22	
General disorders and administration site conditions Fatigue alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	109 / 619 (17.61%) 122	50 / 303 (16.50%) 53	
Asthenia alternative dictionary used:			

MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	62 / 619 (10.02%)	30 / 303 (9.90%)	
occurrences (all)	72	34	
Pyrexia			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	44 / 619 (7.11%)	29 / 303 (9.57%)	
occurrences (all)	52	34	
Oedema Peripheral			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	33 / 619 (5.33%)	29 / 303 (9.57%)	
occurrences (all)	33	31	
Gastrointestinal disorders			
Diarrhoea			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	284 / 619 (45.88%)	34 / 303 (11.22%)	
occurrences (all)	407	38	
Nausea			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	138 / 619 (22.29%)	51 / 303 (16.83%)	
occurrences (all)	170	63	
Constipation			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	88 / 619 (14.22%)	63 / 303 (20.79%)	
occurrences (all)	99	69	
Vomiting			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			

subjects affected / exposed	82 / 619 (13.25%)	36 / 303 (11.88%)	
occurrences (all)	106	50	
Stomatitis			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	34 / 619 (5.49%)	13 / 303 (4.29%)	
occurrences (all)	37	14	
Abdominal Pain			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	26 / 619 (4.20%)	19 / 303 (6.27%)	
occurrences (all)	28	19	
Respiratory, thoracic and mediastinal disorders			
Cough			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	108 / 619 (17.45%)	54 / 303 (17.82%)	
occurrences (all)	122	59	
Dyspnoea			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	98 / 619 (15.83%)	52 / 303 (17.16%)	
occurrences (all)	102	56	
Skin and subcutaneous tissue disorders			
Rash			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	258 / 619 (41.68%)	33 / 303 (10.89%)	
occurrences (all)	295	35	
Pruritus			
alternative dictionary used: MedDRA 12.1			
alternative assessment type: Systematic			
subjects affected / exposed	70 / 619 (11.31%)	16 / 303 (5.28%)	
occurrences (all)	83	16	

Dry Skin alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	49 / 619 (7.92%) 55	8 / 303 (2.64%) 8	
Psychiatric disorders Insomnia alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	63 / 619 (10.18%) 68	24 / 303 (7.92%) 24	
Renal and urinary disorders Proteinuria alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	56 / 619 (9.05%) 66	10 / 303 (3.30%) 13	
Musculoskeletal and connective tissue disorders Back Pain alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	54 / 619 (8.72%) 59	19 / 303 (6.27%) 22	
Musculoskeletal Pain alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	22 / 619 (3.55%) 22	20 / 303 (6.60%) 21	
Metabolism and nutrition disorders Decreased Appetite alternative dictionary used: MedDRA 12.1 alternative assessment type: Systematic subjects affected / exposed occurrences (all)	143 / 619 (23.10%) 158	63 / 303 (20.79%) 67	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2007	Procedural clarifications for ECG, archival tumour samples and patients taking contraindicated concomitant medications. Schedule of assessments clarification for RECIST assessments, collection of AE/SAEs. Clarification on statistical analyses, DMC requirements
16 April 2009	Procedural clarifications. Clarification of secondary endpoints for PRO analysis. Remove co-primary analysis and adjust significance levels and testing procedures accordingly.
08 January 2010	Update to prodecures for patients still receiving treatment after final planned data analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported