



## Clinical trial results:

### A Phase III, Randomised, Double-Blind, Multi-Centre Parallel-Group Study to Assess the Efficacy of Vandetanib (ZD6474, ZACTIMA™) Versus Erlotinib (TARCEVA®) in Patients With Locally Advanced or Metastatic (Stage IIIB – IV) Non-Small Cell Lung Cancer (NSCLC) after Failure of at least One Prior Cytotoxic Chemotherapy

#### Summary

EudraCT number	2006-000259-16
Trial protocol	NL DK NO ES DE IT GB
Global end of trial date	15 November 2016

#### Results information

Result version number	v1 (current)
This version publication date	15 December 2017
First version publication date	15 December 2017

#### Trial information

##### Trial identification

Sponsor protocol code	D4200C000057
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00364351
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Genzyme Corporation
Sponsor organisation address	500 Kendall Street , Cambridge, MA, United States, 02142
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	15 November 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 November 2016
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 demonstrate an improvement in Progression Free Survival (PFS) for vandetanib compared with erlotinib (Tarceva®) in subjects with locally advanced or metastatic NSCLC after failure of at least one but no more than two, prior cytotoxic chemotherapy regimens.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 August 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 34
Country: Number of subjects enrolled	Australia: 60
Country: Number of subjects enrolled	Brazil: 53
Country: Number of subjects enrolled	Canada: 58
Country: Number of subjects enrolled	China: 89
Country: Number of subjects enrolled	Hong Kong: 50
Country: Number of subjects enrolled	India: 32
Country: Number of subjects enrolled	Indonesia: 25
Country: Number of subjects enrolled	Korea, Republic of: 45
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Philippines: 38
Country: Number of subjects enrolled	Taiwan: 51
Country: Number of subjects enrolled	Thailand: 106
Country: Number of subjects enrolled	United States: 148
Country: Number of subjects enrolled	Netherlands: 31
Country: Number of subjects enrolled	Norway: 37
Country: Number of subjects enrolled	Spain: 40

Country: Number of subjects enrolled	United Kingdom: 112
Country: Number of subjects enrolled	Denmark: 20
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	Germany: 62
Country: Number of subjects enrolled	Italy: 86
Worldwide total number of subjects	1240
EEA total number of subjects	435

Notes:

<b>Subjects enrolled per age group</b>	
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)	789
From 65 to 84 years	448
85 years and over	3

## Subject disposition

### Recruitment

Recruitment details:

First subject enrolled 24 August 2006, last subject enrolled 31 October 2007, cut off date 26 September 2008. 1574 subjects were enrolled in the study.

### Pre-assignment

Screening details:

1574 subjects were enrolled/screened to the study but only 1240 subjects were entered treatment/randomized. Completed subjects refers to on going study treatment at data cut-off date 26 Sep 2008.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Vandetanib

Arm description:

Vandetanib 300 mg tablet taken once daily plus a placebo for erlotinib.

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

Dosage and administration details:

Vandetanib was administered each morning, at least 1 hour prior to or 2 hours after, intake of food.

Investigational medicinal product name	Placebo for Erlotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for erlotinib was administered each morning, at least 1 hour prior to or 2 hours after, intake of food.

<b>Arm title</b>	Erlotinib
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Arm description:

Erlotinib 150 mg tablet taken once daily plus a placebo for vandetanib.

Arm type	Active comparator
Investigational medicinal product name	Erlotinib
Investigational medicinal product code	
Other name	Tarceva®
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Erlotinib was administered each morning, at least 1 hour prior to or 2 hours after, intake of food.

Investigational medicinal product name	Placebo for Vandetanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo for vandetanib was administered each morning, at least 1 hour prior to or 2 hours after, intake of food.

<b>Number of subjects in period 1</b>	Vandetanib	Erlotinib
Started	623	617
Completed	31	34
Not completed	592	583
Consent withdrawn by subject	30	29
Randomised treatment not started	-	3
Poor treatment compliance	-	3
Investigator error	-	2
Condition under investigation worsened	469	497
Adverse event	90	44
Incorrect enrollment	1	1
Subject could not travel to site	-	1
Lost to follow-up	1	1
Sponsor decision	1	-
Prohibited concomitant medication	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Vandetanib
Reporting group description: Vandetanib 300 mg tablet taken once daily plus a placebo for erlotinib.	
Reporting group title	Erlotinib
Reporting group description: Erlotinib 150 mg tablet taken once daily plus a placebo for vandetanib.	

Reporting group values	Vandetanib	Erlotinib	Total
Number of subjects	623	617	1240
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60	61	
full range (min-max)	26 to 92	26 to 85	-
Gender categorical Units: Subjects			
Female	242	224	466
Male	381	393	774

## End points

### End points reporting groups

Reporting group title	Vandetanib
Reporting group description: Vandetanib 300 mg tablet taken once daily plus a placebo for erlotinib.	
Reporting group title	Erlotinib
Reporting group description: Erlotinib 150 mg tablet taken once daily plus a placebo for vandetanib.	

### Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS) <sup>[1]</sup>
End point description: Median time (in weeks) from randomisation until objective disease progression or death (by any cause in the absence of objective progression) provided death is within 3 months from the last evaluable Response Evaluation Criteria In Solid Tumors (RECIST) assessment. Progression was derived according to RECIST 1.0 and is defined as an increase of at least 20% in the total tumour size of measurable lesions over the nadir measurement, unequivocal progression in the non-target lesions or the appearance of one or more new lesions.	
End point type	Primary
End point timeframe: progression RECIST tumour assessments carried out every 4 weeks up to week 16 then every 8 weeks thereafter from randomisation until the date of first documented objective disease progression or date of death from any cause, whichever came first, assessed	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive statistics were reported, inferential statistics were not planned to be reported for primary endpoint.

End point values	Vandetanib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	617		
Units: Weeks				
median (full range (min-max))	11.3 (0.14 to 75.43)	8.9 (0.43 to 80.43)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: Overall survival is defined as the time from date of randomization until death. Any subject not known to have died at the time of analysis was censored based on the last recorded date on which the subject was known to be alive (i.e. their status must be known at the censored date and should not be lost to follow up or unknown).	
End point type	Secondary

End point timeframe:  
Time to death in months

End point values	Vandetanib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	617		
Units: Months				
median (full range (min-max))	6.9 (0.03 to 18.46)	7.8 (0.10 to 20.04)		

### 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 subjects that are responders i.e. those subjects with a confirmed best objective response of complete response (CR) or partial response (PR) as determined according to RECIST 1.0. CR is defined as the disappearance of all target lesions with no evidence of tumour elsewhere and PR is defined as at least a 30% reduction in the total tumour size of measurable lesions with no new lesions and no progression in the non-target lesions.	
End point type	Secondary
End point timeframe: RECIST tumour assessments every 4 weeks up to week 16 then every 8 weeks thereafter from randomisation until the date of first documented objective disease progression or date of death from any cause, whichever came first, assessed up to 21 months	

End point values	Vandetanib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	617		
Units: subjects	75	74		

### 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 subjects who achieved disease control at least 8 weeks following randomisation. Disease control is defined as a best objective response of complete response (CR), partial response (PR) or stable disease (SD) $\geq 8$ weeks as determined according to RECIST 1.0.	



CR is defined as the disappearance of all target lesions with no evidence of tumour elsewhere, PR is defined as at least a 30% reduction in the total tumour size of measurable lesions with no new lesions and no progression in the non-target lesions and SD  $\geq 8$  is assigned to subjects who have not responded and have no evidence of progression at least 8 weeks after randomisation.

End point type	Secondary
End point timeframe:	
RECIST tumour assessments carried out every 4 weeks until week 16 then every 8 weeks thereafter (+/-3 days) from randomisation until objective progression	

End point values	Vandetanib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	617		
Units: subjects	254	242		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Deterioration of Disease-related Symptoms (TDS) by EORTC Quality of Life Questionnaire - Pain

End point title	Time to Deterioration of Disease-related Symptoms (TDS) by EORTC Quality of Life Questionnaire - Pain
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End point description:

Pain was assessed as the average score of two items: Question 9 ("Have you had pain") and 19 ("Did pain interfere with your daily activities") of the QLQ-C30. Time to deterioration in symptoms is defined as the interval from the date of randomization to the first assessment of worsened without an improvement in the next 28 days. A subject is defined as having a deterioration in symptoms if they have a single visit assessment of 'worsened' with no visit assessment of 'improved' within the next 28 days. Analysis was performed on FAS, which included all randomized subjects.

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), every 4 weeks thereafter, at discontinuation of study treatment and at the 30-day follow-up visit	

End point values	Vandetanib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	617		
Units: Weeks				
median (inter-quartile range (Q1-Q3))	11.1 (4.4 to 26)	9.9 (4.3 to 24.3)		

## Statistical analyses

## Secondary: Time to Deterioration of Disease-related Symptoms (TDS) by EORTC Quality of Life Questionnaire - Dyspnoea

End point title	Time to Deterioration of Disease-related Symptoms (TDS) by EORTC Quality of Life Questionnaire - Dyspnoea
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### End point description:

Dyspnea was assessed as the average score of four items: Question 8 of the QLQ-C30 ("Were you short of breath") and Question 3 of the QLQ-C30 ("Were you short of breath when you rested"), Questions 4 ("Were you short of breath when you walked") and 5 ("Were you short of breath when you climbed stairs") of the QLQ-LC13 (or, equivalently, Questions 33, 34 and 35 of the combined QLQ-C30 and QLQ-LC13 questionnaires).

Time to deterioration in symptoms is defined as the interval from the date of randomization to the first assessment of worsened without an improvement in the next 28 days. A subject is defined as having a deterioration in symptoms if they have a single visit assessment of 'worsened' with no visit assessment of 'improved' within the next 28 days. Analysis was performed on FAS, which included all randomized subjects.

End point type	Secondary
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### End point timeframe:

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

End point values	Vandetanib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	617		
Units: Weeks				
median (inter-quartile range (Q1-Q3))	12 (5.7 to 29.7)	12.4 (5.1 to 34.4)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Deterioration of Disease-related Symptoms (TDS) by EORTC Quality of Life Questionnaire - Cough

End point title	Time to Deterioration of Disease-related Symptoms (TDS) by EORTC Quality of Life Questionnaire - Cough
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### End point description:

Cough was assessed using Question 1 ("How much did you cough") of the QLQ-LC13 (or, equivalently, Question 31 of the combined QLQ-C30 and QLQ-LC13 questionnaires). Time to deterioration in symptoms is defined as the interval from the date of randomization to the first assessment of worsened without an improvement in the next 28 days. A subject is defined as having a deterioration in symptoms if they have a single visit assessment of 'worsened' with no visit assessment of 'improved' within the next 28 days.

End point type	Secondary
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### End point timeframe:

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

<b>End point values</b>	Vandetanib	Erlotinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	623	617		
Units: Weeks				
median (inter-quartile range (Q1-Q3))	15.6 (8.1 to 36.1)	14.1 (7 to 37.6)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (up to 10 years) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

The Safety Analysis Set included all randomized subjects who received at least 1 dose of randomized treatment, 623 in vandetanib and 614 in erlotinib.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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### Reporting groups

Reporting group title	Vandetanib
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Reporting group description: -

Reporting group title	Erlotinib
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Reporting group description:

Erlotinib.

Serious adverse events	Vandetanib	Erlotinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	197 / 623 (31.62%)	155 / 614 (25.24%)	
number of deaths (all causes)	413	416	
number of deaths resulting from adverse events	36	18	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-Cell Small Lymphocytic Lymphoma			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer Pain			
subjects affected / exposed	3 / 623 (0.48%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	1 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangiosis Carcinomatosa			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Pleural Effusion			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate Cancer			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	1 / 623 (0.16%)	5 / 614 (0.81%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	3 / 623 (0.48%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 623 (0.00%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic Shock			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Jugular Vein Thrombosis			

subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic Hypotension			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Arterial Occlusive Disease			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral Ischaemia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian Vein Thrombosis			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Thoracotomy			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 623 (0.64%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	4 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	2 / 623 (0.32%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chills			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication Associated With Device			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	3 / 623 (0.48%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
Fatigue			
subjects affected / exposed	3 / 623 (0.48%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	3 / 623 (0.48%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal Inflammation			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Non-Cardiac Chest Pain			

subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema Peripheral			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 623 (1.12%)	6 / 614 (0.98%)	
occurrences causally related to treatment / all	1 / 7	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden Death			
subjects affected / exposed	1 / 623 (0.16%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Immune system disorders			
Anaphylactic Shock			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (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			
Acquired Tracheo-Oesophageal Fistula			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	



Acute Respiratory Failure			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthmatic Crisis			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial Fistula			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	4 / 623 (0.64%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	13 / 623 (2.09%)	20 / 614 (3.26%)	
occurrences causally related to treatment / all	1 / 13	3 / 20	
deaths causally related to treatment / all	1 / 6	1 / 2	
Haemoptysis			

subjects affected / exposed	1 / 623 (0.16%)	11 / 614 (1.79%)	
occurrences causally related to treatment / all	1 / 1	4 / 11	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hypoxia			
subjects affected / exposed	0 / 623 (0.00%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial Lung Disease			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal Oedema			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung Infiltration			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	1 / 623 (0.16%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural Fibrosis			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Aspiration			

subjects affected / exposed	2 / 623 (0.32%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonitis			
subjects affected / exposed	2 / 623 (0.32%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	0 / 623 (0.00%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	8 / 623 (1.28%)	6 / 614 (0.98%)	
occurrences causally related to treatment / all	4 / 8	1 / 6	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pulmonary Haemorrhage			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Distress			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Failure			
subjects affected / exposed	3 / 623 (0.48%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Stridor			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed Suicide			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Confusional State			
subjects affected / exposed	1 / 623 (0.16%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental Status Changes			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Body Temperature Increased			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-Reactive Protein Increased			
subjects affected / exposed	0 / 623 (0.00%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram Qt Prolonged			
subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram St-T Change			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T Wave Inversion			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
International Normalised Ratio Increased			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight Decreased			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral Neck Fracture			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur Fracture			
subjects affected / exposed	2 / 623 (0.32%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Radiation			

subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head Injury			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip Fracture			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Post Procedural Haemorrhage			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural Pain			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation Injury			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Compression Fracture			

subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural Haematoma			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular Graft Occlusion			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Fibrillation			
subjects affected / exposed	2 / 623 (0.32%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Arrest			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac Failure			

subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardio-Respiratory Arrest			
subjects affected / exposed	3 / 623 (0.48%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary Failure			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial Infarction			
subjects affected / exposed	6 / 623 (0.96%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	3 / 6	1 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pericardial Effusion			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postinfarction Angina			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right Ventricular Failure			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus Tachycardia			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			



subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torsade De Pointes			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Fibrillation			
subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular Tachycardia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered State Of Consciousness			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aphasia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ataxia			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Infarction			

subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Ischaemia			
subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Thrombosis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	1 / 623 (0.16%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dizziness			
subjects affected / exposed	3 / 623 (0.48%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Lethargy			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis Recurrent Laryngeal Nerve			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychomotor Hyperactivity			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	7 / 623 (1.12%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	3 / 7	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Somnolence			
subjects affected / exposed	0 / 623 (0.00%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech Disorder			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Cord Compression			
subjects affected / exposed	0 / 623 (0.00%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 623 (0.16%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	1 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	1 / 623 (0.16%)	5 / 614 (0.81%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	4 / 623 (0.64%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 623 (0.00%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic Thrombocytopenic Purpura			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Eye disorders			
Ulcerative Keratitis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal Pain			
subjects affected / exposed	4 / 623 (0.64%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Wall Haematoma			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis Ischaemic			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	19 / 623 (3.05%)	8 / 614 (1.30%)	
occurrences causally related to treatment / all	10 / 19	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	4 / 623 (0.64%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	1 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal Ulcer Haemorrhage			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal Hernia Strangulated			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 623 (0.80%)	5 / 614 (0.81%)	
occurrences causally related to treatment / all	3 / 5	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal Stenosis			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small Intestinal Obstruction			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	9 / 623 (1.44%)	9 / 614 (1.47%)	
occurrences causally related to treatment / all	3 / 9	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary Colic			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioedema			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis Acneiform			
subjects affected / exposed	0 / 623 (0.00%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis Exfoliative			
subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema Asteatotic			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema Multiforme			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Photosensitivity Reaction			
subjects affected / exposed	3 / 623 (0.48%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	7 / 623 (1.12%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	7 / 7	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash Erythematous			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash Maculo-Papular			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash Papular			
subjects affected / exposed	0 / 623 (0.00%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus Urinary			



subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial Nephritis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Retention			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 623 (0.00%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone Pain			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular Weakness			
subjects affected / exposed	1 / 623 (0.16%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal Chest Pain			
subjects affected / exposed	3 / 623 (0.48%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck Pain			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain In Extremity			
subjects affected / exposed	0 / 623 (0.00%)	3 / 614 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal Pain			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (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			
Abscess Limb			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis Bacterial			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical Pneumonia			

subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 623 (0.32%)	2 / 614 (0.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium Colitis			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis Clostridial			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Genital Infection			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary Infection			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes Zoster			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective Exacerbation Of Chronic Obstructive Airways Disease			
subjects affected / exposed	2 / 623 (0.32%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection			
subjects affected / exposed	7 / 623 (1.12%)	6 / 614 (0.98%)	
occurrences causally related to treatment / all	0 / 7	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung Infection			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycobacterial Infection			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic Infection			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Infection			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Infection Bacterial			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal Sepsis			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	27 / 623 (4.33%)	22 / 614 (3.58%)	
occurrences causally related to treatment / all	1 / 27	2 / 22	
deaths causally related to treatment / all	0 / 9	1 / 5	
Pneumonia Haemophilus			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Sepsis			

subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary Tuberculosis			
subjects affected / exposed	2 / 623 (0.32%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory Tract Infection			
subjects affected / exposed	5 / 623 (0.80%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	1 / 5	0 / 4	
deaths causally related to treatment / all	1 / 2	0 / 0	
Sepsis			
subjects affected / exposed	1 / 623 (0.16%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic Shock			
subjects affected / exposed	1 / 623 (0.16%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Streptococcal Bacteraemia			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous Abscess			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			

subjects affected / exposed	6 / 623 (0.96%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 623 (0.16%)	0 / 614 (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			
Cachexia			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decreased Appetite			
subjects affected / exposed	3 / 623 (0.48%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	7 / 623 (1.12%)	4 / 614 (0.65%)	
occurrences causally related to treatment / all	1 / 7	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes Mellitus Inadequate Control			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 623 (0.00%)	1 / 614 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 623 (0.32%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	3 / 623 (0.48%)	0 / 614 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Vandetanib	Erlotinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	539 / 623 (86.52%)	542 / 614 (88.27%)	
Investigations			
Weight Decreased			
subjects affected / exposed	33 / 623 (5.30%)	29 / 614 (4.72%)	
occurrences (all)	33	29	
Vascular disorders			
Hypertension			
subjects affected / exposed	99 / 623 (15.89%)	14 / 614 (2.28%)	
occurrences (all)	102	17	
Nervous system disorders			
Dizziness			
subjects affected / exposed	37 / 623 (5.94%)	40 / 614 (6.51%)	
occurrences (all)	39	46	
Headache			
subjects affected / exposed	55 / 623 (8.83%)	40 / 614 (6.51%)	
occurrences (all)	55	44	
General disorders and administration site conditions			
Asthenia			



subjects affected / exposed	50 / 623 (8.03%)	59 / 614 (9.61%)	
occurrences (all)	58	65	
Fatigue			
subjects affected / exposed	119 / 623 (19.10%)	109 / 614 (17.75%)	
occurrences (all)	123	119	
Oedema Peripheral			
subjects affected / exposed	21 / 623 (3.37%)	34 / 614 (5.54%)	
occurrences (all)	21	35	
Pyrexia			
subjects affected / exposed	44 / 623 (7.06%)	50 / 614 (8.14%)	
occurrences (all)	51	53	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	58 / 623 (9.31%)	87 / 614 (14.17%)	
occurrences (all)	63	92	
Diarrhoea			
subjects affected / exposed	300 / 623 (48.15%)	232 / 614 (37.79%)	
occurrences (all)	450	347	
Dyspepsia			
subjects affected / exposed	29 / 623 (4.65%)	31 / 614 (5.05%)	
occurrences (all)	31	31	
Nausea			
subjects affected / exposed	138 / 623 (22.15%)	131 / 614 (21.34%)	
occurrences (all)	157	158	
Stomatitis			
subjects affected / exposed	33 / 623 (5.30%)	33 / 614 (5.37%)	
occurrences (all)	33	36	
Vomiting			
subjects affected / exposed	85 / 623 (13.64%)	91 / 614 (14.82%)	
occurrences (all)	108	113	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	78 / 623 (12.52%)	92 / 614 (14.98%)	
occurrences (all)	84	105	
Dyspnoea			

subjects affected / exposed occurrences (all)	84 / 623 (13.48%) 87	70 / 614 (11.40%) 75	
Haemoptysis subjects affected / exposed occurrences (all)	31 / 623 (4.98%) 32	39 / 614 (6.35%) 45	
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	45 / 623 (7.22%) 49	50 / 614 (8.14%) 59	
Dermatitis Acneiform subjects affected / exposed occurrences (all)	75 / 623 (12.04%) 80	103 / 614 (16.78%) 117	
Dry Skin subjects affected / exposed occurrences (all)	60 / 623 (9.63%) 62	84 / 614 (13.68%) 91	
Pruritus subjects affected / exposed occurrences (all)	38 / 623 (6.10%) 41	67 / 614 (10.91%) 78	
Rash subjects affected / exposed occurrences (all)	169 / 623 (27.13%) 198	232 / 614 (37.79%) 262	
Renal and urinary disorders			
Proteinuria subjects affected / exposed occurrences (all)	33 / 623 (5.30%) 37	8 / 614 (1.30%) 9	
Psychiatric disorders			
Insomnia subjects affected / exposed occurrences (all)	59 / 623 (9.47%) 60	40 / 614 (6.51%) 40	
Musculoskeletal and connective tissue disorders			
Back Pain subjects affected / exposed occurrences (all)	37 / 623 (5.94%) 39	40 / 614 (6.51%) 44	
Musculoskeletal Chest Pain subjects affected / exposed occurrences (all)	33 / 623 (5.30%) 36	24 / 614 (3.91%) 24	

Infections and infestations Paronychia subjects affected / exposed occurrences (all)	12 / 623 (1.93%) 12	31 / 614 (5.05%) 36	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	114 / 623 (18.30%) 125	123 / 614 (20.03%) 127	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 September 2006	Added option to continue blinded vandetanib/erlotinib after progression.
23 April 2007	Subjects receiving medications at study entry on a specific list in the protocol, that have a risk of QTc prolongation but no clear association with torsade de pointes, were allowed to continue those medications. Subjects receiving these medications were excluded if the screening QTc is $\geq 460$ ms, and an additional ECG was obtained 4–8 h after the first dose of vandetanib.
23 April 2007	Exclusion criterion for serum creatinine $>1.5 \times$ ULRR or creatinine clearance $\leq 50$ mL/min changed to creatinine clearance $\leq 30$ mL/min.
19 March 2008	Removed co-primary analysis population.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Primary results are complemented by Sanofi following sponsorship transfer from Astra Zeneca to Sanofi in May 2016, only SAEs are updated per protocol.

Notes: