Clinical trial results:
A Randomised, Double-Blind, Placebo-Controlled, Multi-Centre Phase III Study to Assess the Efficacy and Safety of Vandetanib (CAPRELSA™) 300 mg in Patients with Differentiated Thyroid Cancer That Is Either Locally Advanced or Metastatic Who Are Refractory or Unsuitable for Radioiodine (RAI) Therapy

Summary

EudraCT number	2013-000422-58
Trial protocol	CZ SE IT ES DK FR
Global end of trial date	22 January 2022

Results information

Result version number	v1 (current)
This version publication date	11 August 2024
First version publication date	11 August 2024

Trial information

Trial identification

Sponsor protocol code	D4203C00011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01876784
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Genzyme Research and Development
Sponsor organisation address	500 Kendall Street, Cambridge, 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	19 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 January 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy (as assessed by progression free survival [PFS]) of vandetanib when compared to placebo in subjects with differentiated thyroid cancer that was either locally advanced or metastatic who were refractory or unsuitable for radioiodine therapy.

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	17 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 52
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	China: 22
Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Japan: 40
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	238
EEA total number of subjects	118

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)	117
From 65 to 84 years	117
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 60 active centers in 12 countries. A total of 299 subjects were screened between 17 September 2013 and 26 September 2014 of which 238 subjects were randomised.

Pre-assignment

Screening details:

A total of 235 subjects were treated in the study.

Period 1

Period 1 title	Randomized Treatment Period (40 Months)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Vandetanib

Arm description:

Subjects received vandetanib 300 mg tablet, orally once daily until disease progression or death, in randomised treatment period (up to maximum of 40 months).

Arm type	Experimental
Investigational medicinal product name	Vandetanib
Investigational medicinal product code	SAR390530
Other name	CAPRELSA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vandetanib 300 mg tablet, orally once daily for up to 40 months.

Arm title	Placebo

Arm description:

Subjects received placebo matched to vandetanib tablet, orally once daily until disease progression or death, in randomised treatment period (up to maximum of 40 months).

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:

Subjects received placebo matched to vandetanib 300 mg tablet, orally once daily for up to 40 months.

Number of subjects in period 1	Vandetanib	Placebo
Started	119	119
Treated	117	118
Completed	0	0
Not completed	119	119
Other than specified above	24	25
Consent withdrawn by subject	20	4
Disease progression	43	81
Development of study-specific discontinuation	5	2
Death	1	-
Adverse event	22	5
Randomised but not treated	2	1
Lost to follow-up	1	1
Protocol deviation	1	-

Period 2

Period 2 title	Open-label Period (31 Months)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Vandetanib/Vandetanib

Arm description:

Subjects who completed the randomised treatment period, were offered the opportunity to continue the same vandetanib treatment in the open label period, if, in the investigator's opinion, they received benefit and if the subject agreed and provided their informed consent to continue the open-label period for up to additional 31 months.

Arm type	Experimental
Investigational medicinal product name	Vandetanib
Investigational medicinal product code	SAR390530
Other name	CAPRELSA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vandetanib 300 mg tablet, orally once daily for up to additional 31 months.

Arm title	Placebo/Vandetanib

Arm description:

Subjects who completed the randomised treatment period, and experienced disease progression were offered the option of treatment in open-label period with vandetanib, if in the investigator's opinion, such treatment was of clinical benefit to the subject, and if the subject agreed and provided their informed consent to begin open-label vandetanib treatment (i.e., 300 mg tablet, orally once daily for up to 31 months).

Arm type	Experimental
Investigational medicinal product name	Vandetanib
Investigational medicinal product code	SAR390530
Other name	CAPRELSA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received vandetanib 300 mg tablet, orally once daily for up to additional 31 months.

Number of subjects in period 2	Vandetanib/Vandetanib	Placebo/Vandetanib
Started	23	74
Completed	0	0
Not completed	23	74
Other than specified above	9	18
Consent withdrawn by subject	6	8
Development of study-specific discontinuation	1	5
Death	-	1
Adverse event	2	6
Progressive disease	4	35
Lost to follow-up	1	-
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Vandetanib
Reporting group description:	
Subjects received vandetanib 300 mg tablet, orally once daily until disease progression or death, in randomised treatment period (up to maximum of 40 months).	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to vandetanib tablet, orally once daily until disease progression or death, in randomised treatment period (up to maximum of 40 months).	

Reporting group values	Vandetanib	Placebo	Total
Number of subjects	119	119	238
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 64.2 ± 9.69	 63.2 ± 11.02	 -
Gender categorical Units: Subjects			
Female	70	64	134
Male	49	55	104

End points

End points reporting groups

Reporting group title	Vandetanib
Reporting group description:	
Subjects received vandetanib 300 mg tablet, orally once daily until disease progression or death, in randomised treatment period (up to maximum of 40 months).	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to vandetanib tablet, orally once daily until disease progression or death, in randomised treatment period (up to maximum of 40 months).	
Reporting group title	Vandetanib/Vandetanib
Reporting group description:	
Subjects who completed the randomised treatment period, were offered the opportunity to continue the same vandetanib treatment in the open label period, if, in the investigator's opinion, they received benefit and if the subject agreed and provided their informed consent to continue the open-label period for up to additional 31 months.	
Reporting group title	Placebo/Vandetanib
Reporting group description:	
Subjects who completed the randomised treatment period, and experienced disease progression were offered the option of treatment in open-label period with vandetanib, if in the investigator's opinion, such treatment was of clinical benefit to the subject, and if the subject agreed and provided their informed consent to begin open-label vandetanib treatment (i.e., 300 mg tablet, orally once daily for up to 31 months).	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
The PFS was defined as the time (in months) from randomisation until the date of first documented disease progression or death (from any cause), whichever came first. Disease progression as per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) was defined as: at least a 20% increase and absolute increase of 5 mm in the sum of the longest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Analysis was performed by Kaplan-Meier method. Intent to treat population included all randomised subjects.	
End point type	Primary
End point timeframe:	
Randomisation until disease progression or death, assessed every 12 weeks (up to 22 months)	

End point values	Vandetanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: months				
median (confidence interval 95%)	10.0 (6.0 to 11.1)	5.7 (5.5 to 8.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis for Progression-Free Survival

Statistical analysis description:

A multiple testing procedure (MTP) with an alpha-exhaustive recycling strategy was employed to provide adequate control of type I error.

Comparison groups	Placebo v Vandetanib
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.03

Notes:

[1] - Threshold for significance at 0.05 level.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomisation until death due to any cause. In the absence of observation of death, survival time was censored to last date the subject was known to be alive or at the cut-off date, whichever comes first. Analysis was performed by Kaplan-Meier method. Analysis was performed on intent-to-treat population. Here, "9999" and "99999" were used as space filler which denotes median & 95% CI lower limit respectively were not estimable due to insufficient number of subjects with events.

End point type	Secondary

End point timeframe:

From randomisation to the date of death due to any cause (maximum duration: up to 42 months)

End point values	Vandetanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: months				
median (confidence interval 95%)	9999 (31.6 to 99999)	9999 (32.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Randomised Treatment Period: Percent Change From Baseline in Tumor Size (TS) at Week 36

End point title	Randomised Treatment Period: Percent Change From Baseline

	in Tumor Size (TS) at Week 36

End point description:

Tumor size was the sum of the longest diameters of the target lesions. Target lesions were measurable tumor lesions. Baseline was defined as the last evaluable assessment prior to starting treatment. Analysis was performed on intent-to-treat population. Here, 'number of subjects analysed' = subjects evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline, Week 36

End point values	Vandetanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	116		
Units: percent change				
arithmetic mean (standard deviation)	23.29 (± 50.059)	21.52 (± 25.428)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects With Objective Response

End point title	Percentage of subjects With Objective Response

End point description:

Objective Response was defined as the percentage (%) of subjects with complete response or partial response. Per RECIST 1.1 criteria, complete response was defined as the disappearance of all target lesions since Baseline. Any pathological lymph nodes selected as target lesions must have a reduction in short axis to less than (<)10 millimeters (mm). Partial response was defined as at least a 30% decrease in the sum of the diameters of target lesions, taking as reference the Baseline sum of diameters. Progressive Disease was defined as at least at least a 20% increase and absolute increase of 5 mm in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. Analysis was performed on intent-to-treat population. Here, 'number of subjects analysed' = subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

From randomisation to the date of first documented tumor progression, or death due to any cause, whichever comes first (maximum duration: up to 42 months)

End point values	Vandetanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	118		
Units: percentage of subjects				
number (not applicable)	5.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Worsening of Pain (TWP) Using Numeric Rating Scale (NRS) of Worst Pain

End point title	Time to Worsening of Pain (TWP) Using Numeric Rating Scale (NRS) of Worst Pain

End point description:

Time to worsening of pain was defined as the time interval from the date of randomisation to the date of first assessment of worsening of pain with no evidence of improvement within the next 14 days. Subjects rate their worst pain intensity during the past seven days using an 11-point NRS scale, where 0 represents "no pain" and 10 represents "pain as bad as you can imagine." Higher scores indicated greater pain severity. TWP analysis was performed using Kaplan-Meier method. Analysis was performed on intent-to-treat population.

End point type	Secondary

End point timeframe:

From randomisation to the date of first assessment of worsening of pain (maximum duration: up to 42 months)

End point values	Vandetanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: months				
median (confidence interval 95%)	5.6 (2.9 to 8.4)	8.3 (2.8 to 16.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response was defined as the time from the date of first documented response until the date of documented progression or death. If subjects did not progress following a response, then their DOR used the PFS censoring time. Per RECIST 1.1, progressive disease was defined as at least a 20% increase and absolute increase of 5 mm in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions. DOR analysis was performed using Kaplan-Meier method. Analysis was performed on subset of subjects with response. Here, "9999" and "99999" were used as space filler which denotes median & 95% CI upper and lower limit respectively were not estimable due an insufficient number of subjects with events.

End point type	Secondary

End point timeframe:

From the date of first response to the date of first documented tumor progression or death due to any cause whichever comes first (maximum duration: up to 42 months)

End point values	Vandetanib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	0[2]		
Units: months				
median (confidence interval 95%)	99999 (-9999 to 99999)	(to)		

Notes:

[2] - '0' signifies that no subject achieved any response, therefore DOR was not analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Randomized Treatment Period: PK Parameters: Maximum Plasma Concentration (Cmax)

End point title	Randomized Treatment Period: PK Parameters: Maximum Plasma Concentration (Cmax)[3]

End point description:

Number of participants analyzed= participants with available data for the time points.

End point type	Secondary

End point timeframe:

Post-dose on Week 1 to Week 48

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is applicable for Vandetanib arm.

End point values	Vandetanib			
Subject group type	Reporting group			
Number of subjects analysed	98			
Units: nanograms per millilitre				
arithmetic mean (standard deviation)				
Week 1 (n=98)	695.1 (± 238.94)			
Week 2 (n=95)	846.2 (± 288.98)			
Week 4 (n=93)	975.7 (± 358.33)			
Week 8 (n=90)	1043.1 (± 395.08)			
Week 12 (n=83)	1041.9 (± 404.69)			
Week 24 (n=61)	1004.9 (± 408.34)			
Week 36 (n=48)	904.1 (± 312.51)			
Week 48 (n=28)	963.0 (± 452.4)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The data for non-serious adverse events are presented until the Last Participant Last Visit (LPLV) date i.e., 19 June 2017, up to 3 years and 9 months. Serious adverse events were collected until the end of the study, up to 8 years and 4 months.

Adverse event reporting additional description:

Analysis was performed for safety population. For participants who continued Vandetanib after the LPLV because they still benefited of it per investigator judgment, Serious adverse events were collected as long as they received treatment. No non-serious adverse events were collected after LPLV for open label period of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Randomized Treatment Period: Vandetanib

Reporting group description:

Subjects received vandetanib 300 mg tablet, orally once daily until disease progression or death, in randomized treatment period (up to maximum of 40 months).

Reporting group title	Randomized Treatment Period: Placebo

Reporting group description:

Subjects received placebo matched to vandetanib tablet, orally once daily until disease progression or death, in randomized treatment period (up to maximum of 40 months).

Reporting group title	Open-Label Treatment Period: Vandetanib/Vandetanib

Reporting group description:

Subjects who completed the randomised treatment period, were offered the opportunity to continue the same vandetanib treatment in the open label period, if in the investigator’s opinion, they received benefit and if the subject agreed and provided their informed consent to continue the open-label period for up to additional 31 months.

Reporting group title	Open-Label Treatment Period: Placebo/Vandetanib

Reporting group description:

Subjects who completed the randomized treatment period, and experienced disease progression were offered the option of treatment in open-label period with vandetanib, if, in the investigator’s opinion, such treatment was of clinical benefit to the subject, and if the subject agreed and provided their informed consent to begin open-label vandetanib treatment i.e., 300 mg tablet, orally once daily for up to 31 months.

Serious adverse events	Randomized Treatment Period: Vandetanib	Randomized Treatment Period: Placebo	Open-Label Treatment Period: Vandetanib/Vandetanib
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 117 (31.62%)	19 / 118 (16.10%)	7 / 23 (30.43%)
number of deaths (all causes)	32	15	9
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			

subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Cancer			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon Cancer			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder Cancer			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma Gastric			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant Neoplasm Progression			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Tumour Haemorrhage			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous Cell Carcinoma Of Lung			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Metastases To Spinal Cord			

subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Varicose Vein			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Impaired Healing			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			

subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 1	0 / 0
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia Aspiration			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pleural Effusion			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 117 (0.85%)	3 / 118 (2.54%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pulmonary Embolism			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Respiratory Failure			
subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood Creatinine Increased			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin Increased			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip Fracture			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypobarism			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur Fracture			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib Fracture			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Haemorrhage			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Atrial Fibrillation			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Flutter			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Arrest			

subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Cardiac Failure Acute			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Ventricular Extrasystoles			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised Tonic-Clonic Seizure			
subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ivth Nerve Paresis			

subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebrobasilar Insufficiency			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 117 (0.85%)	2 / 118 (1.69%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone Marrow Failure			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	3 / 117 (2.56%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal Hernia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 117 (0.00%)	2 / 118 (1.69%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large Intestine Polyp			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumoperitoneum			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Photosensitivity Reaction			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Henoch-Schonlein Purpura			

subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis Bullous			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson Syndrome			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Cystitis Noninfective			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic Syndrome			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Obstruction			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			

Inappropriate Antidiuretic Hormone Secretion			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Muscular Weakness			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal Chest Pain			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological Fracture			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 117 (3.42%)	2 / 118 (1.69%)	1 / 23 (4.35%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	2 / 2	1 / 1	0 / 0
Lung Infection			
subjects affected / exposed	2 / 117 (1.71%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Lung Abscess			

subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Procedural Infection			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 117 (0.00%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory Tract Infection			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin Infection			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 117 (0.00%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary Tract Infection			

subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 117 (0.85%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Open-Label Treatment Period: Placebo/Vandetanib		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 74 (32.43%)		
number of deaths (all causes)	27		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric Cancer				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon Cancer				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bladder Cancer				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Adenocarcinoma Gastric				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Malignant Neoplasm Progression				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour Haemorrhage				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous Cell Carcinoma Of Lung				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metastases To Spinal Cord				

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Varicose Vein			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease Progression			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple Organ Dysfunction Syndrome			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Impaired Healing			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute Respiratory Failure			

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Chronic Obstructive Pulmonary Disease				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia Aspiration				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Interstitial Lung Disease				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory Failure				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
Psychiatric disorders				
Depression				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood Creatinine Increased				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Troponin Increased				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fall				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hip Fracture				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Hypobarism				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Femur Fracture				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rib Fracture				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Post Procedural Haemorrhage				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Myocardial Infarction				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial Flutter				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular Block				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Arrest				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac Failure Acute				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular Extrasystoles				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Dizziness				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epilepsy				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Generalised Tonic-Clonic Seizure				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic Stroke				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ivth Nerve Paresis				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Somnolence				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vertebrobasilar Insufficiency				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bone Marrow Failure				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal Pain				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Inguinal Hernia				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large Intestine Polyp				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumoperitoneum				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholelithiasis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Photosensitivity Reaction				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Henoch-Schonlein Purpura				

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dermatitis Bullous			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Rash			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stevens-Johnson Syndrome			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis Noninfective			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrotic Syndrome			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary Tract Obstruction			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			

Inappropriate Antidiuretic Hormone Secretion				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscular Weakness				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal Chest Pain				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pathological Fracture				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Pneumonia				
subjects affected / exposed	4 / 74 (5.41%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	3 / 3			
Lung Infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	1 / 1			
Lung Abscess				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Post Procedural Infection				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory Tract Infection				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin Infection				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Upper Respiratory Tract Infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection				

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Randomized Treatment Period: Vandetanib	Randomized Treatment Period: Placebo	Open-Label Treatment Period: Vandetanib/Vandetanib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 117 (94.87%)	87 / 118 (73.73%)	9 / 23 (39.13%)
Vascular disorders			

Hypertension			
subjects affected / exposed	48 / 117 (41.03%)	9 / 118 (7.63%)	0 / 23 (0.00%)
occurrences (all)	53	9	0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 117 (5.13%)	10 / 118 (8.47%)	0 / 23 (0.00%)
occurrences (all)	7	14	0
Non-Cardiac Chest Pain			
subjects affected / exposed	3 / 117 (2.56%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	13 / 117 (11.11%)	13 / 118 (11.02%)	1 / 23 (4.35%)
occurrences (all)	14	13	1
Asthenia			
subjects affected / exposed	21 / 117 (17.95%)	15 / 118 (12.71%)	1 / 23 (4.35%)
occurrences (all)	27	15	1
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	3 / 117 (2.56%)	6 / 118 (5.08%)	0 / 23 (0.00%)
occurrences (all)	3	7	0
Dyspnoea			
subjects affected / exposed	7 / 117 (5.98%)	10 / 118 (8.47%)	0 / 23 (0.00%)
occurrences (all)	7	10	0
Dysphonia			
subjects affected / exposed	3 / 117 (2.56%)	4 / 118 (3.39%)	0 / 23 (0.00%)
occurrences (all)	3	4	0
Cough			
subjects affected / exposed	11 / 117 (9.40%)	12 / 118 (10.17%)	1 / 23 (4.35%)
occurrences (all)	11	16	1
Haemoptysis			
subjects affected / exposed	4 / 117 (3.42%)	8 / 118 (6.78%)	0 / 23 (0.00%)
occurrences (all)	5	9	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 117 (12.82%)	2 / 118 (1.69%)	0 / 23 (0.00%)
occurrences (all)	15	2	0

Anxiety			
subjects affected / exposed	6 / 117 (5.13%)	5 / 118 (4.24%)	0 / 23 (0.00%)
occurrences (all)	6	5	0
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	15 / 117 (12.82%)	4 / 118 (3.39%)	0 / 23 (0.00%)
occurrences (all)	21	7	0
Alanine Aminotransferase Increased			
subjects affected / exposed	16 / 117 (13.68%)	4 / 118 (3.39%)	0 / 23 (0.00%)
occurrences (all)	23	6	0
Blood Creatinine Increased			
subjects affected / exposed	7 / 117 (5.98%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences (all)	9	1	0
Electrocardiogram Qt Prolonged			
subjects affected / exposed	36 / 117 (30.77%)	4 / 118 (3.39%)	1 / 23 (4.35%)
occurrences (all)	55	6	1
Weight Decreased			
subjects affected / exposed	10 / 117 (8.55%)	3 / 118 (2.54%)	0 / 23 (0.00%)
occurrences (all)	11	4	0
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 117 (13.68%)	9 / 118 (7.63%)	0 / 23 (0.00%)
occurrences (all)	23	11	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 117 (5.13%)	6 / 118 (5.08%)	1 / 23 (4.35%)
occurrences (all)	7	8	1
Eye disorders			
Cornea Verticillata			
subjects affected / exposed	9 / 117 (7.69%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences (all)	9	0	1
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	9 / 117 (7.69%)	11 / 118 (9.32%)	2 / 23 (8.70%)
occurrences (all)	11	13	2
Abdominal Pain Upper			

subjects affected / exposed	6 / 117 (5.13%)	4 / 118 (3.39%)	1 / 23 (4.35%)
occurrences (all)	9	4	1
Abdominal Pain			
subjects affected / exposed	8 / 117 (6.84%)	8 / 118 (6.78%)	0 / 23 (0.00%)
occurrences (all)	9	9	0
Diarrhoea			
subjects affected / exposed	77 / 117 (65.81%)	24 / 118 (20.34%)	3 / 23 (13.04%)
occurrences (all)	126	29	5
Dry Mouth			
subjects affected / exposed	6 / 117 (5.13%)	2 / 118 (1.69%)	1 / 23 (4.35%)
occurrences (all)	6	2	1
Dyspepsia			
subjects affected / exposed	6 / 117 (5.13%)	3 / 118 (2.54%)	0 / 23 (0.00%)
occurrences (all)	7	4	0
Nausea			
subjects affected / exposed	22 / 117 (18.80%)	17 / 118 (14.41%)	1 / 23 (4.35%)
occurrences (all)	24	21	1
Vomiting			
subjects affected / exposed	9 / 117 (7.69%)	12 / 118 (10.17%)	1 / 23 (4.35%)
occurrences (all)	14	15	1
Stomatitis			
subjects affected / exposed	6 / 117 (5.13%)	3 / 118 (2.54%)	0 / 23 (0.00%)
occurrences (all)	6	3	0
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	6 / 117 (5.13%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences (all)	7	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 117 (5.13%)	2 / 118 (1.69%)	0 / 23 (0.00%)
occurrences (all)	6	3	0
Acne			
subjects affected / exposed	9 / 117 (7.69%)	2 / 118 (1.69%)	0 / 23 (0.00%)
occurrences (all)	9	2	0
Pruritus			

subjects affected / exposed	6 / 117 (5.13%)	5 / 118 (4.24%)	1 / 23 (4.35%)
occurrences (all)	6	5	1
Photosensitivity Reaction			
subjects affected / exposed	14 / 117 (11.97%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences (all)	15	0	0
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	6 / 117 (5.13%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences (all)	7	0	0
Erythema			
subjects affected / exposed	5 / 117 (4.27%)	2 / 118 (1.69%)	0 / 23 (0.00%)
occurrences (all)	7	2	0
Dry Skin			
subjects affected / exposed	18 / 117 (15.38%)	6 / 118 (5.08%)	0 / 23 (0.00%)
occurrences (all)	18	6	0
Dermatitis Acneiform			
subjects affected / exposed	13 / 117 (11.11%)	2 / 118 (1.69%)	0 / 23 (0.00%)
occurrences (all)	14	2	0
Rash			
subjects affected / exposed	36 / 117 (30.77%)	6 / 118 (5.08%)	0 / 23 (0.00%)
occurrences (all)	51	7	0
Rash Maculo-Papular			
subjects affected / exposed	7 / 117 (5.98%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences (all)	7	1	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	8 / 117 (6.84%)	0 / 118 (0.00%)	1 / 23 (4.35%)
occurrences (all)	8	0	1
Haematuria			
subjects affected / exposed	7 / 117 (5.98%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences (all)	7	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 117 (5.98%)	5 / 118 (4.24%)	0 / 23 (0.00%)
occurrences (all)	11	5	0
Musculoskeletal Chest Pain			

subjects affected / exposed	8 / 117 (6.84%)	9 / 118 (7.63%)	0 / 23 (0.00%)
occurrences (all)	10	9	0
Back Pain			
subjects affected / exposed	8 / 117 (6.84%)	12 / 118 (10.17%)	2 / 23 (8.70%)
occurrences (all)	9	14	2
Musculoskeletal Pain			
subjects affected / exposed	0 / 117 (0.00%)	10 / 118 (8.47%)	0 / 23 (0.00%)
occurrences (all)	0	11	0
Infections and infestations			
Paronychia			
subjects affected / exposed	3 / 117 (2.56%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences (all)	3	1	0
Conjunctivitis			
subjects affected / exposed	1 / 117 (0.85%)	0 / 118 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	8 / 117 (6.84%)	7 / 118 (5.93%)	0 / 23 (0.00%)
occurrences (all)	10	9	0
Urinary Tract Infection			
subjects affected / exposed	11 / 117 (9.40%)	3 / 118 (2.54%)	0 / 23 (0.00%)
occurrences (all)	16	4	0
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 117 (4.27%)	7 / 118 (5.93%)	0 / 23 (0.00%)
occurrences (all)	5	8	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	21 / 117 (17.95%)	2 / 118 (1.69%)	1 / 23 (4.35%)
occurrences (all)	23	2	1
Hypokalaemia			
subjects affected / exposed	9 / 117 (7.69%)	5 / 118 (4.24%)	0 / 23 (0.00%)
occurrences (all)	11	5	0
Hypomagnesaemia			
subjects affected / exposed	9 / 117 (7.69%)	1 / 118 (0.85%)	0 / 23 (0.00%)
occurrences (all)	19	1	0
Hypocalcaemia			

subjects affected / exposed	17 / 117 (14.53%)	3 / 118 (2.54%)	1 / 23 (4.35%)
occurrences (all)	18	3	1

Non-serious adverse events	Open-Label Treatment Period: Placebo/Vandetanib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 74 (83.78%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	31 / 74 (41.89%)		
occurrences (all)	35		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Non-Cardiac Chest Pain			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	14 / 74 (18.92%)		
occurrences (all)	14		
Asthenia			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal Pain			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
Dysphonia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Cough			

subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	14		
Haemoptysis			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	11		
Anxiety			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	10		
Alanine Aminotransferase Increased			
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	13		
Blood Creatinine Increased			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Electrocardiogram Qt Prolonged			
subjects affected / exposed	20 / 74 (27.03%)		
occurrences (all)	36		
Weight Decreased			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		

Eye disorders			
Cornea Verticillata			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	1		
Abdominal Pain Upper			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Abdominal Pain			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	39 / 74 (52.70%)		
occurrences (all)	58		
Dry Mouth			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Dyspepsia			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	16 / 74 (21.62%)		
occurrences (all)	20		
Vomiting			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	7		
Stomatitis			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	1		
Acne			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Pruritus			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	6		
Photosensitivity Reaction			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Palmar-Plantar Erythrodysaesthesia Syndrome			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Erythema			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	7		
Dry Skin			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Dermatitis Acneiform			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	9		
Rash			
subjects affected / exposed	19 / 74 (25.68%)		
occurrences (all)	24		
Rash Maculo-Papular			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	5		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
Haematuria			

subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
Musculoskeletal Chest Pain			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	7		
Back Pain			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	1		
Musculoskeletal Pain			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Infections and infestations			
Paronychia			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Conjunctivitis			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Nasopharyngitis			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Urinary Tract Infection			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
Upper Respiratory Tract Infection			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	15 / 74 (20.27%)		
occurrences (all)	19		
Hypokalaemia			

subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	11		
Hypomagnesaemia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2013	Following changes were made: The inclusion criteria were updated to include patients with follicular DTC (except minimally invasive follicular DTC); clarification was added that subjects who received blinded vandetanib prior to progression required re-consent at central confirmation of progression in order to permit dosing with open-label vandetanib.
29 February 2016	Following changes were made: The study sponsorship was transferred to Sanofi Genzyme.
01 July 2016	Following changes were made: The requirement to follow subjects for overall survival until >=50% of subjects had died was lowered to >=25% subjects' deaths.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study was part of the drug acquisition where model-based PK analysis was not performed by the legacy company. Available PK descriptive statistics have been reported.

Notes: