Clinical trial results:
A Randomized, Double Blind, Placebo-Controlled Phase II, Multi-Centre Study to Assess the Efficacy and Safety of Zactima™ in Patients with Advanced or Metastatic Papillary or Follicular Thyroid Carcinoma Failing or Unsuitable for Radioiodine Therapy

Summary

EudraCT number	2007-001890-27
Trial protocol	FR DK SE ES BE PT
Global end of trial date	24 November 2021

Results information

Result version number	v1 (current)
This version publication date	16 December 2023
First version publication date	16 December 2023

Trial information

Trial identification

Sponsor protocol code	D4200C00079

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00537095
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi-Aventis Recherche & Développement
Sponsor organisation address	1 Avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
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	31 March 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate an improvement in progression free survival (PFS) with ZACTIMA™ (ZD6474) 300 milligrams (mg) as compared to placebo in subjects with advanced or metastatic papillary or follicular thyroid carcinoma failing 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	29 September 2007
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	Switzerland: 18
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 17
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Denmark: 10
Country: Number of subjects enrolled	France: 76
Worldwide total number of subjects	145
EEA total number of subjects	127

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)	77
From 65 to 84 years	67
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

From September 28th, 2007 to October 16th, 2008, 145 subjects were randomised by 16 active centers in 7 European countries to receive vandetanib 300 mg once daily oral dose or placebo.

Pre-assignment

Screening details:

The main reason for non-randomisation was non-respect of eligibility criteria.

Period 1

Period 1 title	Randomised Treatment Period (433 days)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	ZD6474

Arm description:

ZD6474, Vandetanib 300 mg

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

Dosage and administration details:

Subjects received Vandetanib 300 mg tablet, orally once daily.

Arm title	PLACEBO

Arm description:

Placebo

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.

Number of subjects in period 1	ZD6474	PLACEBO
Started	72	73
Completed	0	0
Not completed	72	73
Objective Disease Progression	21	48
Adverse Event	24	4
As per protocol (after 12 m of blinded treatment)	21	16
Death	3	1
Withdrawal by Subject	2	2
Subjective/ Clinic Progression or Lack of Efficacy	1	2

Period 2

Period 2 title	Open-label Period (590 days)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	ZD6474/ ZD6474

Arm description:

Subjects still receiving vandetanib (ZD6474) at the end of the trial were offered the opportunity to enter the open-label phase and continue to vandetanib (ZD6474) as long as they still benefitted of it per investigator's judgement or until subsequent ant-cancer therapy.

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

Dosage and administration details:

Subjects received Vandetanib 300 mg tablet, orally once daily.

Arm title	PLACEBO/ ZD6474

Arm description:

Subjects who experienced disease progression during the randomized period were offered to enter the open-label phase and received vandetanib (ZD6474) as long as they benefitted of it or until subsequent anti-cancer therapy.

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

Dosage and administration details:
Subjects received Vandetanib 300 mg tablet, orally once daily.

Number of subjects in period 2	ZD6474/ ZD6474	PLACEBO/ ZD6474
Started	28	59
Completed	16	20
Not completed	12	39
Objective Disease Progression	2	21
Adverse Event	2	11
Death	2	2
Withdrawal by Subject	1	2
Subjective/Clinic Progression or Lack of Efficacy	5	3

Baseline characteristics

Reporting groups	
Reporting group title	ZD6474
Reporting group description: ZD6474, Vandetanib 300 mg	
Reporting group title	PLACEBO
Reporting group description: Placebo	

Reporting group values	ZD6474	PLACEBO	Total
Number of subjects	72	73	145
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.8	63.8	
standard deviation	± 11.21	± 11.59	-
Gender categorical Units: Subjects			
Female	33	34	67
Male	39	39	78

End points

End points reporting groups

Reporting group title	ZD6474
Reporting group description:	
ZD6474, Vandetanib 300 mg	
Reporting group title	PLACEBO
Reporting group description:	
Placebo	
Reporting group title	ZD6474/ ZD6474
Reporting group description:	
Subjects still receiving vandetanib (ZD6474) at the end of the trial were offered the opportunity to enter the open-label phase and continue to vandetanib (ZD6474) as long as they still benefitted of it per investigator's judgement or until subsequent ant-cancer therapy.	
Reporting group title	PLACEBO/ ZD6474
Reporting group description:	
Subjects who experienced disease progression during the randomized period were offered to enter the open-label phase and received vandetanib (ZD6474) as long as they benefitted of it or until subsequent anti-cancer therapy.	

Primary: Time to Tumor Progression

End point title	Time to Tumor Progression[1]
End point description:	
modified RECIST V1.0 was used.	
End point type	Primary
End point timeframe:	
Time from date of randomisation to date of the first documented tumor progression or date of death from any cause (within the 3 months) of tumor assessment	
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: As the endpoint was descriptive in nature, no statistical analysis was performed.	

End point values	ZD6474	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: days				
median (confidence interval 95%)	334 (232 to 421)	176 (119 to 267)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate at 6 Months

End point title	Disease Control Rate at 6 Months
End point description:	
Number of subjects that achieved disease control 6 months after randomisation. Best objective response	

of complete response + partial response + stable disease > 24 weeks according to RECIST criteria.

End point type	Secondary

End point timeframe:

6 months after randomisation

End point values	ZD6474	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: subjects	41	31		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate

End point description:

Best objective response of the subjects from an average of 46.7 months, defined as complete or partial response according to RECIST criteria.

End point type	Secondary

End point timeframe:

46.7 months

End point values	ZD6474	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: subjects	6	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Death

End point title	Time to Death

End point description:

Interim analysis time to date of randomisation to date of death (data not mature at the time of this analysis, so number of deaths displayed instead.

End point type	Secondary

End point timeframe:

time from randomisation to date of death

End point values	ZD6474	PLACEBO		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	73		
Units: subjects	19	21		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation until the end of the study, approximately up to 14 years

Adverse event reporting additional description:

Analysis was performed on the safety population. For subjects who continued Vandetanib after LSLV because they still benefited from it per the investigator's judgment, SAEs were collected as long as they received treatment. No non-serious adverse events were collected after LSLV for the open-label period of the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Randomized Treatment Period: Vandetanib (ZD6474)

Reporting group description:

Subjects received vandetanib (ZD6474) 300 mg orally once daily, until disease progression or until 12 months of stable disease during randomised treatment period, or until the end of the trial whichever comes first.

Reporting group title	Open-Label Treatment Period: Vandetanib/Vandetanib (ZD6474)

Reporting group description:

Subjects still receiving vandetanib (ZD6474) at the end of the trial were offered the opportunity to enter the open label phase and continue to vandetanib (ZD6474) as long as they still benefitted of it per investigator judgement or until subsequent ant-cancer therapy.

Reporting group title	Open-Label Treatment Period: Placebo/Vandetanib (ZD6474)

Reporting group description:

Subjects who experienced disease progression during the randomized period were offered to enter the open-label phase and received vandetanib (ZD6474) as long as they benefitted of it or until subsequent anti-cancer therapy.

Reporting group title	Randomized Treatment Period: Placebo

Reporting group description:

Subjects received placebo matching to vandetanib (ZD6474) tablet orally once daily, until disease progression or until 12 months of stable disease during randomised treatment period, or until the end of the trial whichever occurred first.

Serious adverse events	Randomized Treatment Period: Vandetanib (ZD6474)	Open-Label Treatment Period: Vandetanib/Vandetanib (ZD6474)	Open-Label Treatment Period: Placebo/Vandetanib (ZD6474)
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 73 (27.40%)	12 / 29 (41.38%)	17 / 58 (29.31%)
number of deaths (all causes)	15	5	14
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric Cancer			

subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic Syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Tumour Haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General Physical Health Deterioration			
subjects affected / exposed	1 / 73 (1.37%)	1 / 29 (3.45%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Immune system disorders			
Drug Hypersensitivity			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 73 (2.74%)	0 / 29 (0.00%)	0 / 58 (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
Haemoptysis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial Lung Disease			

subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Lung Disorder			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Pleural Effusion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic Pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Pulmonary Embolism			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Investigations			
Activated Partial Thromboplastin Time Prolonged			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram Qt Prolonged			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Drug Exposure During Pregnancy			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Femur Fracture			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus Fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal Fracture			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia Fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Atrial Fibrillation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Bradyarrhythmia			

subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Sinus Bradycardia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Torsade De Pointes			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Ventricular Tachycardia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Nervous system disorders			
Cerebral Haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Cerebral Infarction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cluster Headache			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			

subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Headache			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic Stroke			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Loss Of Consciousness			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Monoparesis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Spinal Cord Compression			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Syncope			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Transient Ischaemic Attack			

subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 73 (0.00%)	2 / 29 (6.90%)	0 / 58 (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
Ascites			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Inguinal Hernia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Intestinal Obstruction			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Pancreatitis Acute			

subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Rectal Haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Vomiting			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile Duct Obstruction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Acute			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder Rupture			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Cutaneous Lupus Erythematosus			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Photosensitivity Reaction			

subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Rash			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Skin Haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Renal and urinary disorders			
Calculus Urinary			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal Failure			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Back Pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Flank Pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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

Groin Pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Muscular Weakness			
subjects affected / exposed	1 / 73 (1.37%)	2 / 29 (6.90%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Bronchitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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
Bronchopneumonia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	0 / 58 (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
Catheter Related Infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue Fever			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 73 (2.74%)	1 / 29 (3.45%)	3 / 58 (5.17%)
occurrences causally related to treatment / all	2 / 2	0 / 1	1 / 3
deaths causally related to treatment / all	1 / 1	1 / 1	1 / 1
Sepsis			

subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Urinary Tract Infection Viral			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (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			
Hypocalcaemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (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
Tumour Lysis Syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	0 / 58 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0

Serious adverse events	Randomized Treatment Period: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 72 (16.67%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric Cancer			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic Syndrome			

subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tumour Haemorrhage				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
General Physical Health Deterioration				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Drug Hypersensitivity				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial Lung Disease				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lung Disorder				

subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural Effusion				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pleuritic Pain				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Activated Partial Thromboplastin Time Prolonged				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram Qt Prolonged				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Drug Exposure During Pregnancy				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femur Fracture				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Humerus Fracture				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal Fracture				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia Fracture				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Angina Pectoris				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arrhythmia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrioventricular Block				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradyarrhythmia				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sinus Bradycardia				

subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Torsade De Pointes				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ventricular Tachycardia				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebral Haemorrhage				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral Infarction				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cluster Headache				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Convulsion				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				

subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ischaemic Stroke				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Loss Of Consciousness				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Monoparesis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal Cord Compression				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient Ischaemic Attack				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Lymphadenopathy				

subjects affected / exposed	0 / 72 (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 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal Hernia				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intestinal Obstruction				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis Acute				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal Haemorrhage				

subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Bile Duct Obstruction				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis Acute				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gallbladder Rupture				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Cutaneous Lupus Erythematosus				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Photosensitivity Reaction				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash				

subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin Haemorrhage				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Calculus Urinary				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal Failure				
subjects affected / exposed	0 / 72 (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	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back Pain				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Flank Pain				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Groin Pain				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Muscular Weakness				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Appendicitis				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchopneumonia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Catheter Related Infection				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dengue Fever				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 72 (1.39%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Sepsis				
subjects affected / exposed	0 / 72 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urinary Tract Infection Viral				

subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour Lysis Syndrome			
subjects affected / exposed	0 / 72 (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 (ZD6474)	Open-Label Treatment Period: Vandetanib/Vandetanib (ZD6474)	Open-Label Treatment Period: Placebo/Vandetanib (ZD6474)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 73 (98.63%)	17 / 29 (58.62%)	54 / 58 (93.10%)
Vascular disorders			
Peripheral Coldness			
subjects affected / exposed	0 / 73 (0.00%)	2 / 29 (6.90%)	0 / 58 (0.00%)
occurrences (all)	0	2	0
Hypertension			
subjects affected / exposed	25 / 73 (34.25%)	1 / 29 (3.45%)	19 / 58 (32.76%)
occurrences (all)	26	1	19
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 73 (26.03%)	2 / 29 (6.90%)	10 / 58 (17.24%)
occurrences (all)	19	2	12
Chest Pain			

subjects affected / exposed	4 / 73 (5.48%)	0 / 29 (0.00%)	4 / 58 (6.90%)
occurrences (all)	4	0	4
Fatigue			
subjects affected / exposed	17 / 73 (23.29%)	3 / 29 (10.34%)	9 / 58 (15.52%)
occurrences (all)	19	3	9
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 73 (5.48%)	2 / 29 (6.90%)	7 / 58 (12.07%)
occurrences (all)	4	2	7
Dysphonia			
subjects affected / exposed	4 / 73 (5.48%)	1 / 29 (3.45%)	5 / 58 (8.62%)
occurrences (all)	4	1	6
Epistaxis			
subjects affected / exposed	5 / 73 (6.85%)	1 / 29 (3.45%)	1 / 58 (1.72%)
occurrences (all)	6	1	1
Dyspnoea			
subjects affected / exposed	5 / 73 (6.85%)	2 / 29 (6.90%)	2 / 58 (3.45%)
occurrences (all)	5	2	3
Haemoptysis			
subjects affected / exposed	3 / 73 (4.11%)	0 / 29 (0.00%)	3 / 58 (5.17%)
occurrences (all)	3	0	3
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 73 (6.85%)	1 / 29 (3.45%)	4 / 58 (6.90%)
occurrences (all)	5	1	4
Depression			
subjects affected / exposed	8 / 73 (10.96%)	1 / 29 (3.45%)	1 / 58 (1.72%)
occurrences (all)	8	1	1
Insomnia			
subjects affected / exposed	8 / 73 (10.96%)	0 / 29 (0.00%)	5 / 58 (8.62%)
occurrences (all)	8	0	5
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	2 / 73 (2.74%)	0 / 29 (0.00%)	5 / 58 (8.62%)
occurrences (all)	2	0	5
Electrocardiogram Qt Prolonged			

subjects affected / exposed	16 / 73 (21.92%)	2 / 29 (6.90%)	5 / 58 (8.62%)
occurrences (all)	17	2	5
Weight Decreased			
subjects affected / exposed	13 / 73 (17.81%)	1 / 29 (3.45%)	6 / 58 (10.34%)
occurrences (all)	13	1	6
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 73 (16.44%)	2 / 29 (6.90%)	4 / 58 (6.90%)
occurrences (all)	13	2	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 29 (3.45%)	2 / 58 (3.45%)
occurrences (all)	0	1	2
Leukopenia			
subjects affected / exposed	4 / 73 (5.48%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences (all)	4	0	1
Neutropenia			
subjects affected / exposed	4 / 73 (5.48%)	1 / 29 (3.45%)	0 / 58 (0.00%)
occurrences (all)	5	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	9 / 73 (12.33%)	1 / 29 (3.45%)	3 / 58 (5.17%)
occurrences (all)	12	1	3
Eye disorders			
Conjunctivitis			
subjects affected / exposed	4 / 73 (5.48%)	0 / 29 (0.00%)	2 / 58 (3.45%)
occurrences (all)	4	0	2
Vision Blurred			
subjects affected / exposed	5 / 73 (6.85%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences (all)	5	0	1
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	9 / 73 (12.33%)	0 / 29 (0.00%)	6 / 58 (10.34%)
occurrences (all)	10	0	6
Abdominal Pain Upper			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	2 / 58 (3.45%)
occurrences (all)	1	0	3

Cheilitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	3 / 58 (5.17%)
occurrences (all)	1	0	3
Constipation			
subjects affected / exposed	5 / 73 (6.85%)	4 / 29 (13.79%)	5 / 58 (8.62%)
occurrences (all)	5	4	5
Diarrhoea			
subjects affected / exposed	53 / 73 (72.60%)	5 / 29 (17.24%)	40 / 58 (68.97%)
occurrences (all)	66	6	41
Dry Mouth			
subjects affected / exposed	5 / 73 (6.85%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences (all)	5	0	1
Dyspepsia			
subjects affected / exposed	4 / 73 (5.48%)	1 / 29 (3.45%)	1 / 58 (1.72%)
occurrences (all)	4	1	1
Nausea			
subjects affected / exposed	18 / 73 (24.66%)	1 / 29 (3.45%)	11 / 58 (18.97%)
occurrences (all)	21	1	12
Vomiting			
subjects affected / exposed	6 / 73 (8.22%)	0 / 29 (0.00%)	4 / 58 (6.90%)
occurrences (all)	7	0	4
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	20 / 73 (27.40%)	1 / 29 (3.45%)	14 / 58 (24.14%)
occurrences (all)	21	1	15
Alopecia			
subjects affected / exposed	4 / 73 (5.48%)	1 / 29 (3.45%)	3 / 58 (5.17%)
occurrences (all)	4	1	3
Dermatitis Acneiform			
subjects affected / exposed	6 / 73 (8.22%)	0 / 29 (0.00%)	2 / 58 (3.45%)
occurrences (all)	6	0	2
Dry Skin			
subjects affected / exposed	12 / 73 (16.44%)	0 / 29 (0.00%)	3 / 58 (5.17%)
occurrences (all)	12	0	3
Eczema			

subjects affected / exposed	4 / 73 (5.48%)	0 / 29 (0.00%)	0 / 58 (0.00%)
occurrences (all)	5	0	0
Erythema			
subjects affected / exposed	5 / 73 (6.85%)	1 / 29 (3.45%)	4 / 58 (6.90%)
occurrences (all)	9	1	4
Photosensitivity Reaction			
subjects affected / exposed	13 / 73 (17.81%)	1 / 29 (3.45%)	3 / 58 (5.17%)
occurrences (all)	16	1	3
Pigmentation Disorder			
subjects affected / exposed	6 / 73 (8.22%)	0 / 29 (0.00%)	0 / 58 (0.00%)
occurrences (all)	8	0	0
Pruritus			
subjects affected / exposed	4 / 73 (5.48%)	0 / 29 (0.00%)	6 / 58 (10.34%)
occurrences (all)	4	0	7
Rash			
subjects affected / exposed	17 / 73 (23.29%)	0 / 29 (0.00%)	11 / 58 (18.97%)
occurrences (all)	17	0	11
Skin Disorder			
subjects affected / exposed	2 / 73 (2.74%)	2 / 29 (6.90%)	1 / 58 (1.72%)
occurrences (all)	2	2	1
Skin Lesion			
subjects affected / exposed	4 / 73 (5.48%)	0 / 29 (0.00%)	4 / 58 (6.90%)
occurrences (all)	4	0	5
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 73 (1.37%)	2 / 29 (6.90%)	2 / 58 (3.45%)
occurrences (all)	1	2	2
Back Pain			
subjects affected / exposed	4 / 73 (5.48%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences (all)	5	0	1
Bone Pain			
subjects affected / exposed	3 / 73 (4.11%)	0 / 29 (0.00%)	3 / 58 (5.17%)
occurrences (all)	3	0	3
Muscle Spasms			

subjects affected / exposed	1 / 73 (1.37%)	1 / 29 (3.45%)	3 / 58 (5.17%)
occurrences (all)	1	1	3
Myalgia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	1 / 58 (1.72%)
occurrences (all)	1	0	1
Pain In Extremity			
subjects affected / exposed	6 / 73 (8.22%)	0 / 29 (0.00%)	0 / 58 (0.00%)
occurrences (all)	6	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 73 (5.48%)	1 / 29 (3.45%)	2 / 58 (3.45%)
occurrences (all)	4	1	2
Folliculitis			
subjects affected / exposed	7 / 73 (9.59%)	1 / 29 (3.45%)	5 / 58 (8.62%)
occurrences (all)	9	1	5
Nasopharyngitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 29 (0.00%)	0 / 58 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	19 / 73 (26.03%)	2 / 29 (6.90%)	9 / 58 (15.52%)
occurrences (all)	20	2	9
Hypocalcaemia			
subjects affected / exposed	6 / 73 (8.22%)	1 / 29 (3.45%)	6 / 58 (10.34%)
occurrences (all)	7	1	6
Hypokalaemia			
subjects affected / exposed	9 / 73 (12.33%)	0 / 29 (0.00%)	2 / 58 (3.45%)
occurrences (all)	11	0	3

Non-serious adverse events	Randomized Treatment Period: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	65 / 72 (90.28%)		
Vascular disorders			
Peripheral Coldness			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		

Hypertension			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 72 (22.22%)		
occurrences (all)	21		
Chest Pain			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	13 / 72 (18.06%)		
occurrences (all)	13		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 72 (12.50%)		
occurrences (all)	9		
Dysphonia			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	9 / 72 (12.50%)		
occurrences (all)	11		
Haemoptysis			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		

Insomnia subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 3		
Investigations Alanine Aminotransferase Increased subjects affected / exposed occurrences (all) Electrocardiogram Qt Prolonged subjects affected / exposed occurrences (all) Weight Decreased subjects affected / exposed occurrences (all)	 0 / 72 (0.00%) 0 0 / 72 (0.00%) 0 5 / 72 (6.94%) 5		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 14 / 72 (19.44%) 14		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	 4 / 72 (5.56%) 5 0 / 72 (0.00%) 0 0 / 72 (0.00%) 0		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 7 / 72 (9.72%) 7		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all) Vision Blurred	 1 / 72 (1.39%) 1 		

subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	6		
Abdominal Pain Upper			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Cheilitis			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	12 / 72 (16.67%)		
occurrences (all)	14		
Dry Mouth			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	11 / 72 (15.28%)		
occurrences (all)	11		
Vomiting			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	10		
Alopecia			

subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Dermatitis Acneiform			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Dry Skin			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Eczema			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Photosensitivity Reaction			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Pigmentation Disorder			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		
Skin Disorder			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Skin Lesion			
subjects affected / exposed	0 / 72 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		
Back Pain			
subjects affected / exposed	6 / 72 (8.33%)		
occurrences (all)	7		
Bone Pain			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Muscle Spasms			
subjects affected / exposed	2 / 72 (2.78%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Pain In Extremity			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	5		
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 72 (6.94%)		
occurrences (all)	6		
Folliculitis			
subjects affected / exposed	3 / 72 (4.17%)		
occurrences (all)	3		
Nasopharyngitis			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	10 / 72 (13.89%)		
occurrences (all)	11		
Hypocalcaemia			
subjects affected / exposed	4 / 72 (5.56%)		
occurrences (all)	4		
Hypokalaemia			

subjects affected / exposed occurrences (all)	3 / 72 (4.17%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 September 2007	Following changes were done: Title page was updated to clarify the diagnosis for subjects, protocol synopsis and study design were updated to clarify the radiologic evaluation. Ophthalmologic examinations were added to help determine if ZD6474 increased the likelihood for a subject to develop corneal opacities in the study plan. Exclusion criteria was updated and randomisation procedure was updated in section Method of assigning subjects to treatment groups. In the section, blinding and procedures for unblinding the study, clarification was added to unblinding procedure. Clarification of the concomitant medications not allowed during the study was added in the 'Other concomitant treatment' section. Clarification of the Routine haematology and biochemistry assessments performed in local laboratory in the section 'Methods of assessment.'
09 November 2007	Following changes were done: In the section Protocol Synopsis and study design it was updated that the all the subjects (both active and placebo) were unblinded and given the option to study treatment and enter follow up and survival, or begin open label vandetanib 300 mg treatment, and not upon disease progression. In the section Other toxicity, it was updated to stop the study drug in case of Grade 3 or 4 diarrhoea. In the section, Inclusion Criteria, clarification in target lesion baseline was added and in section, exclusion criteria, clarification on prior treatment with a kinase inhibitor was added.
21 January 2008	Following changes were done: In the sections Protocol Synopsis and Study Design, it was clarified that the subjects would be unblinded only if they entered the open label period. In the section Rationale for study design, doses and control groups, it was added that the dose reduction would be possible in case of grade 3-4 toxicities to ensure the safety of the subject and avoid high number of drop-outs and Appendix L was created. In the section, Inclusion Criteria, updates were made to clarify the measurable lesion size at Baseline and to improve compliance with the country specific reference ranges. In the section Method is assigning subjects to treatment groups, it was updated that if a subject was a screen failure, it was possible to re-screen the subject. Section Data and Safety Monitoring Board was updated to ensure the safety of subjects and validity & integrity of the data. It may include the appointment of independent Data Safety Monitoring Board.
18 June 2009	Following changes were made: In the section, ' Rationale for study design, doses and control groups', the rationale for treating the subjects with 300 mg vandetanib /Placebo every other day in case of dose reduction was added. To ensure compliance and safety of the subject was decided to create a new label for the study drug for potential subjects on dose reduction in the open label of the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported