Clinical trial results:
A Phase II, Open-Label Study To Assess The Efficacy and Tolerability of ZD6474 (ZACTIMA) 100mg Monotherapy In Subjects with Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer

Summary

EudraCT number	2006-001354-28
Trial protocol	NL ES IT
Global end of trial date	30 May 2014

Results information

Result version number	v1 (current)
This version publication date	21 May 2016
First version publication date	21 May 2016

Trial information

Trial identification

Sponsor protocol code	D4200C00068

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Lisa McCormack, AstraZeneca Pharmaceuticals. LP, +44 01625 5151063, lisa.mccormack@astrazeneca.com
Scientific contact	Gabriella Mariani, AstraZeneca Pharmaceuticals. LP, +44 07818523899, gabriella.mariani@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 July 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2008
Global end of trial reached?	Yes
Global end of trial date	30 May 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the objective response rate in patients treated with vandetanib 100 mg monotherapy.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 August 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Italy: 7
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	22
EEA total number of subjects	14

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)	19
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	22
Number of subjects completed	19

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Incorrect enrollment: 2
Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not Applicable

Arms

Arm title	Vandetanib 100mg

Arm description:

Vandetanib 100mg per day

Arm type	Experimental
Investigational medicinal product name	ZD6474
Investigational medicinal product code	F013025
Other name	ZACTIMA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 100mg tablet to be taken whole, orally per day.

Number of subjects in period 1[1]	Vandetanib 100mg
Started	19
Completed	19

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 22 patients were enrolled worldwide but 3 patients did not pass screening – 2 had the

incorrect enrolment and 1 withdrew their consent, thus only 19 patients entered the baseline period which is less than the number enrolled.

Period 2

Period 2 title	100mg Vandetanib
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Vandetanib 100mg

Arm description:

Vandetanib 100mg per day

Arm type	Experimental
Investigational medicinal product name	ZD6474
Investigational medicinal product code	F013025
Other name	ZACTIMA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 100mg tablet to be taken whole, orally per day.

Number of subjects in period 2	Vandetanib 100mg
Started	19
Completed	11
Not completed	8
Consent withdrawn by subject	1
Adverse event, non-fatal	3
Lack of efficacy	4

Period 3

Period 3 title	Post-Progression Vandetanib 300mg
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not Applicable

Arms

Arm title	Post Progression Treatment

Arm description:

Post progression Vandetanib 300mg per day

Arm type	Experimental
Investigational medicinal product name	ZD6474
Investigational medicinal product code	F013383
Other name	ZACTIMA
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 300mg tablet to be taken whole, orally per day.

Number of subjects in period 3[2]	Post Progression Treatment
Started	4
Completed	3
Not completed	1
Lack of efficacy	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: "Post-progression Van 300mg" part of the study is optional and only 4 of the 19 patients that started the 100mg part, opted to continue on the 300mg, thus the number is less than the 100 mg patient numbers.

Baseline characteristics

Reporting groups	
Reporting group title	Vandetanib 100mg
Reporting group description:	
Vandetanib 100mg per day	

Reporting group values	Vandetanib 100mg	Total	
Number of subjects	19	19	
Age Categorical Units: Subjects			
Adults (18-64 years)	17	17	
From 65-74 years	1	1	
75 years and over	1	1	
Age Continuous Units: years			
arithmetic mean	44.7		
full range (min-max)	22 to 79	-	
Gender Categorical Units: Subjects			
Female	6	6	
Male	13	13	
Race Units: Subjects			
Caucasian	18	18	
Other	1	1	
Ethnic Group Units: Subjects			
Not applicable	17	17	
Native Hawaiian/Pacific islander	1	1	
Other	1	1	
Disease Stage Units: Subjects			
IVA	1	1	
IVC	18	18	
Locally advanced disease sites Units: Subjects			
Lymph nodes	7	7	
Neck	1	1	
Other sites	1	1	
None	10	10	
Previous therapies for MTC Units: Subjects			
Anticancer therapy	6	6	
Radiotherapy	4	4	
Chemotherapy	2	2	
None	7	7	
Family history of MTC			

Units: Subjects			
Yes	14	14	
No	3	3	
Unknown	2	2	
Associated endocrinopathies Units: Subjects			
MEN 2a	17	17	
FMTC	1	1	
MEN 2b	1	1	
RET mutation status Units: Subjects			
Positive	17	17	
Negative	0	0	
Unknown	2	2	
WHO performance status at entry Units: Subjects			
0 (Normal activity)	16	16	
1 (Restricted activity)	1	1	
2 (In bed ≤50% of the time)	2	2	
3 (In bed >50% of the time)	0	0	
4 (100% bedridden)	0	0	
Time since diagnosis Units: years			
arithmetic mean	13		
full range (min-max)	5 to 33	-	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set consisted of all patients who received at least 1 dose of vandetanib.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety analysis set comprised all patients who received at least 1 dose of vandetanib.

Subject analysis set title	PK Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The PK analysis population consisted of all patients who received at least 1 dose of vandetanib.

Reporting group values	Full Analysis Set	Safety Analysis Set	PK Analysis Set
Number of subjects	19	19	19
Age Categorical Units: Subjects			
Adults (18-64 years)	17	17	17
From 65-74 years	1	1	1
75 years and over	1	1	1
Age Continuous Units: years			
arithmetic mean	44.7	44.7	44.7

full range (min-max)	22 to 79	22 to 79	22 to 79

Gender Categorical Units: Subjects			
Female	6	6	6
Male	13	13	13
Race Units: Subjects			
Caucasian	18	18	18
Other	1	1	1
Ethnic Group Units: Subjects			
Not applicable	17	17	17
Native Hawaiian/Pacific islander	1	1	1
Other	1	1	1
Disease Stage Units: Subjects			
IVA	1	1	1
IVC	18	18	18
Locally advanced disease sites Units: Subjects			
Lymph nodes	7	7	7
Neck	1	1	1
Other sites	1	1	1
None	10	10	10
Previous therapies for MTC Units: Subjects			
Anticancer therapy	6	6	6
Radiotherapy	4	4	4
Chemotherapy	2	2	2
None	7	7	7
Family history of MTC Units: Subjects			
Yes	14	14	14
No	3	3	3
Unknown	2	2	2
Associated endocrinopathies Units: Subjects			
MEN 2a	17	17	17
FMTC	1	1	1
MEN 2b	1	1	1
RET mutation status Units: Subjects			
Positive	17	17	17
Negative	0	0	0
Unknown	2	2	2
WHO performance status at entry Units: Subjects			
0 (Normal activity)	16	16	16
1 (Restricted activity)	1	1	1

2 (In bed ≤50% of the time)	2	2	2
3 (In bed >50% of the time)	0	0	0
4 (100% bedridden)	0	0	0
Time since diagnosis			
Units: years			
arithmetic mean	13	13	13
full range (min-max)	5 to 33	5 to 33	5 to 33

End points

End points reporting groups

Reporting group title	Vandetanib 100mg
Reporting group description: Vandetanib 100mg per day	
Reporting group title	Vandetanib 100mg
Reporting group description: Vandetanib 100mg per day	
Reporting group title	Post Progression Treatment
Reporting group description: Post progression Vandetanib 300mg per day	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set consisted of all patients who received at least 1 dose of vandetanib.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: The safety analysis set comprised all patients who received at least 1 dose of vandetanib.	
Subject analysis set title	PK Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The PK analysis population consisted of all patients who received at least 1 dose of vandetanib.	

Primary: Objective Response Rate

End point title	Objective Response Rate[1]
End point description: Responders were those patients with a best objective response of CR or PR. A best response of CR meant that the patient satisfied the criteria for CR on 1 visit,and that the CR status was confirmed by repeat imaging at not less than 4 weeks following the date of identified CR. A best response of PR meant that the patient satisfied the criteria for PR on 1 visit, confirmed by repeat imaging at not less than 4 weeks following the date of PR.	
End point type	Primary
End point timeframe: Best response during 100mg Vandetanib period	

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 this is a small single arm study there are no formal statistical analyses.

End point values	Vandetanib 100mg			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Response - CR	0			
Response - PR	3			
Response - Total	3			
Non response - SD >= 8wks	12			

Non response - PD	3			
Non response - NE	1			
Non response - Total	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

PFS is calculated from the date of first dose until the date of objective progression or death (by any cause in the absence of documented disease progression). Subjects who have not progressed or died at the time of statistical analysis will be censored at the time of their latest objective tumor assessment. This includes subjects who are lost to follow-up or those who have withdrawn consent.

End point type	Secondary

End point timeframe:

PFS during 100mg Vandetanib period

End point values	Vandetanib 100mg			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Progression - RECIST	4			
Progression - Death	1			
Progression - Total	5			
No Progression - Alive	14			
No Progression - Death	0			
No Progression - Lost to FUP	0			
No Progression - Total	14			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate

End point description:

DCR will be based upon data from assessments performed at baseline, during treatment, and at follow-up. DCR will be defined as the percentage of subjects who have a best response of CR, or PR or SD ≥12 weeks.

End point type	Secondary

End point timeframe:

DCR during 100mg Vandetanib period

End point values	Vandetanib 100mg			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Disease Control	13			
No Disease Control	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response

End point title	Duration of Objective Response

End point description:

DOR will be calculated for those subjects who have a best response of CR or PR.DOR will be defined in two ways:1. From date of first documentation of the response until the date of disease progression or death from any cause.2. From date of first dose until the date of disease progression or death from any cause.

End point type	Secondary

End point timeframe:

DOR during the 100mg Vandetanib period

End point values	Vandetanib 100mg			
Subject group type	Reporting group			
Number of subjects analysed	3			
Units: Days				
median (confidence interval 95%)				
Duration of response from onset of response	168 (158 to 245)			
Duration of response from first dose	252 (246 to 400)			
Time to response from first dose	89 (85 to 156)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease Control

End point title	Duration of Disease Control

End point description:

Duration of disease control will be calculated for those subjects who have a best response of CR, PR or SD ≥12 weeks only.Duration of disease control will be defined from date of first dose until the date of disease progression or death from any cause. Any subject who has not progressed or died by the date of data cut-off, or who has been lost to follow up, will be right-censored in the analysis at the date of their last disease assessment.

End point type	Secondary

End point timeframe:

Duration of disease control during the 100mg Vandetanib period

End point values	Vandetanib 100mg			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Days				
median (confidence interval 95%)				
Duration of disease control	256 (246 to 343)			

Statistical analyses

No statistical analyses for this end point

Secondary: Symptomatic Diarrhoea Response

End point title	Symptomatic Diarrhoea Response

End point description:

Symptomatic response will be defined as at least a 50% decrease in the stool frequency (represented by a persistent decrease in stool frequency over 4 weeks), taking as reference the baseline (mean) level.

End point type	Secondary

End point timeframe:

Response during the 100mg Vandetanib period

End point values	Vandetanib 100mg			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Symptomatic Response	0			
No Symptomatic Response	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Objective Response and CTN Biochemical Response

End point title	Best Objective Response and CTN Biochemical Response
End point description:	
BOR based on CTN biochemical response	
End point type	Secondary
End point timeframe:	
CTN response during the 100mg Vandetanib period	

End point values	Vandetanib 100mg			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Response - CR	0			
Response - PR	3			
Response - Total	3			
Non-response - SD	13			
Non-response- PD	2			
Non-response - NE	1			
Non-response - Total	16			

Statistical analyses

No statistical analyses for this end point

Secondary: Best Objective Response and CEA Biochemical Response

End point title	Best Objective Response and CEA Biochemical Response
End point description:	
BOR based on CEA biochemical response	
End point type	Secondary
End point timeframe:	
Response during the 100mg Vandetanib period	

End point values	Vandetanib 100mg			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Subjects				
Response - CR	0			
Response - PR	1			
Response - Total	1			
Non-response - SD	11			

Non-response PD	2			
Non-respons - NE	5			
Non-response - Total	18			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Objective Progression

End point title	Objective Progression

End point description:

End point type	Other pre-specified

End point timeframe:

Including 300mg Vandetanib period

End point values	Post Progression Treatment			
Subject group type	Reporting group			
Number of subjects analysed	4			
Units: Subjects				
Progression - RECIST	1			
Progression - Death	0			
Progression - Total	1			
No Progression - Alive	3			
No Progression - Death	0			
No Progression - Lost to FUP	0			
No Progression - Total	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 1 to end of 60-day follow-up period.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.1

Reporting groups	
Reporting group title	Post Progression Treatment
Reporting group description: Post progression 300mg Vandetanib	
Reporting group title	Vandetanib 100mg
Reporting group description: Vandetanib 100mg per day	

Serious adverse events	Post Progression Treatment	Vandetanib 100mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	4 / 19 (21.05%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Phaechromocytoma			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia Aspiration			
alternative dictionary used: MedDRA 10.1			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endocrine disorders			
Diabetes Disorders			

subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Post Progression Treatment	Vandetanib 100mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	17 / 19 (89.47%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Flushing			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	8 / 19 (42.11%)	
occurrences (all)	0	9	
Asthenia			
subjects affected / exposed	1 / 4 (25.00%)	1 / 19 (5.26%)	
occurrences (all)	1	1	
Influenza Like Illness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Mucous Membrane Disorde			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Thirst			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

Reproductive system and breast disorders			
Erectile Dysfunction			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Menorrhagia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Coughing			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Dysphonia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Dyspnea Exertional			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pharyngolaryngeal Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Upper Respiratory Tract Congestion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Haemoptysi			
subjects affected / exposed	1 / 4 (25.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Investigations			
Weight Decreased			

subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	3	
Electrocardiogram QT Prolonged			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Weight Increased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Dysarthria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Deafness Unilateral			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Diplopia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Visual Disturbance			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Diarrhea NOS			
subjects affected / exposed	1 / 4 (25.00%)	9 / 19 (47.37%)	
occurrences (all)	1	11	
Constipation			
subjects affected / exposed	0 / 4 (0.00%)	4 / 19 (21.05%)	
occurrences (all)	0	4	
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	3	
Abdominal Pain			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Flatulenc			
subjects affected / exposed	1 / 4 (25.00%)	2 / 19 (10.53%)	
occurrences (all)	1	2	
Dry Mouth			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Haemorrhoidal Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Oral Discomfort			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 4 (0.00%)	5 / 19 (26.32%)	
occurrences (all)	0	5	
Photosensitivity reaction (NOS)			

subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	3	
Dermatitis Acneiform			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	4	
Dry Skin			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Acne NOS			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pruritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Rash Erythematou			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Rash Maculo-papular			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Skin Exfoliatio			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Renal Failure			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 4 (0.00%)	3 / 19 (15.79%)	
occurrences (all)	0	3	
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Mobility Decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Muscle Spasms			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Muscular Weakness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Myalg			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Neck Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Infections and infestations			
Folliculitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	2 / 19 (10.53%)	
occurrences (all)	0	2	
Furuncle			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

Paronychia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Tinea Pedis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Upper resp tract infection			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 19 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 4 (25.00%)	3 / 19 (15.79%)	
occurrences (all)	1	3	
Hypocalcemia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 19 (5.26%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2006	Increase number of sites; clarification on post-progression 300mg treatment phase; further explanation of RECIST assessment schedule for subjects discontinuning treatment; increase ECG monitoring for subjects in 300mg treatment period; clarify and make consistent schedule of assessments
09 October 2006	Clarification of schedule of assessments and procedures. Addition of patients with CTCAE Grade 4 HTN having treatment withheld; clarification of administration of treatment; blood sampling schedule and change in personnel
18 November 2009	Include procedures for management of subjects still receiving treatment following final planned analyses.
04 November 2011	Update list of medications with possible risk of TdP; approval of ZD6474 by FDA, additional regulatory approvals pending

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported