Clinical trial results:
A Phase II, Open-Label, Randomized, Multicenter Trial of GW786034 (Pazopanib) in Combination with Lapatinib (GW572016) Compared to Lapatinib Alone as First Line Therapy in Subjects with Advanced or Metastatic Breast Cancer with ErbB2 Fluorescence In Situ Hybridization (FISH) Positive Tumors

Summary

EudraCT number	2005-004350-28
Trial protocol	GB HU
Global end of trial date	14 March 2015

Results information

Result version number	v1 (current)
This version publication date	02 March 2016
First version publication date	02 March 2016

Trial information

Trial identification

Sponsor protocol code	VEG20007

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the rate of disease progression at 12 weeks between pazopanib in combination with lapatinib versus lapatinib alone in subjects with locally advanced or metastatic breast cancer whose tumors are ErbB2 FISH+.

Protection of trial subjects:

Dose modifications for pazopanib were permitted if hypertension, proteinuria, thrombosis or hemorrhage was experienced by the subject and the investigator considered pazopanib may contribute to the event.
Pazopanib dose interruptions or reductions (200mg per time) were permitted.
Dose interruption of pazopanib and lapatinib were permitted for up to 2 weeks in the event of toxicity.
Subjects who experience at least a 20% absolute decrease in left ventricular cardiac ejection fraction (LVEF) from baseline should be monitored. Repeated similar or worsening results should result in lapatinib dose interruption or discontinuation.
Dose interruptions were possible for subjects experiencing liver related treatment emergent AEs as pre-specified in protocol.
Subjects could receive full supportive care during the study, including transfusion of blood and blood products, treatment with antibiotics, analgesics or bisphosphonates, when appropriate.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	24 July 2006
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	United Kingdom: 14
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Pakistan: 25
Country: Number of subjects enrolled	Peru: 38
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 12

Country: Number of subjects enrolled	Singapore: 7
Country: Number of subjects enrolled	Thailand: 1
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	189
EEA total number of subjects	36

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)	159
From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants (par.) were enrolled into two cohorts. Cohort 1: Par. were randomized 1:1 to lapatinib 1500 mg or lapatinib 1000 mg/pazopanib 400 mg. Cohort 2: After enrollment was complete for Cohort 1, par. were enrolled to lapatinib 1500 mg/pazopanib 800 mg. All par. who received study drug are accounted for in the Participant Flow module.

Pre-assignment

Screening details:

Female par. with >=18 years of age with histologically confirmed invasive breast cancer were enrolled in the study. Total 189 par. (Cohort 1, combination n = 76, lapatinib n = 73; Cohort 2, n = 40) received study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Lapatinib 1500 mg

Arm description:

Lapatinib 1500 milligrams (mg) administered orally once a day

Arm type	Active comparator
Investigational medicinal product name	lapatinib (GW572016) 1500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1500 mg administered orally once daily.

Arm title	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg

Arm description:

Lapatinib 1000 mg and Pazopanib 400 mg administered orally once a day

Arm type	Experimental
Investigational medicinal product name	lapatinib (GW572016) 1000 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1000 mg administered orally once daily.

Investigational medicinal product name	pazopanib (GW786034) 400 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400 mg administered orally once daily

Arm title	Cohort 2: Lapatinib 1500 mg/Pazopanib 800 mg

Arm description: Lapatinib 1500 mg and Pazopanib 800 mg administered orally once a day	
Arm type	Experimental
Investigational medicinal product name	lapatinib (GW572016) 1500 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1500 mg administered orally once daily.	
Investigational medicinal product name	pazopanib (GW786034) 800 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 800 mg administered orally once daily	

Number of subjects in period 1	Cohort 1: Lapatinib 1500 mg	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg	Cohort 2: Lapatinib 1500 mg/Pazopanib 800 mg
Started	73	76	40
Completed	2	0	2
Not completed	71	76	38
Physician decision	1	1	-
Consent withdrawn by subject	6	8	-
Death	35	42	19
Par. Started Other Treatment	1	1	1
Lost to follow-up	11	13	-
Missing	2	1	2
Sponsor terminated study	15	10	16

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Lapatinib 1500 mg
Reporting group description: Lapatinib 1500 milligrams (mg) administered orally once a day	
Reporting group title	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg
Reporting group description: Lapatinib 1000 mg and Pazopanib 400 mg administered orally once a day	
Reporting group title	Cohort 2: Lapatinib 1500 mg/Pazopanib 800 mg
Reporting group description: Lapatinib 1500 mg and Pazopanib 800 mg administered orally once a day	

Reporting group values	Cohort 1: Lapatinib 1500 mg	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg	Cohort 2: Lapatinib 1500 mg/Pazopanib 800 mg
Number of subjects	73	76	40
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.7	51.9	55
standard deviation	± 11.23	± 12.48	± 12.71
Gender categorical Units: Subjects			
Female	73	76	40
Male	0	0	0
Race, customized Units: Subjects			
African American/African Heritage	0	2	0
American Indian or Alaska Native	20	18	0
Asian	33	33	4
White	20	22	35
Unknown	0	1	1
Child-Bearing Potential Units: Subjects			
Post-Menopausal	50	51	26
Sterile (of child-bearing age)	3	2	5
Potentially able to bear children	20	23	9

Reporting group values	Total		
Number of subjects	189		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			

standard deviation	-		

Gender categorical Units: Subjects			
Female	189		
Male	0		
Race, customized Units: Subjects			
African American/African Heritage	2		
American Indian or Alaska Native	38		
Asian	70		
White	77		
Unknown	2		
Child-Bearing Potential Units: Subjects			
Post-Menopausal	127		
Sterile (of child-bearing age)	10		
Potentially able to bear children	52		

End points

End points reporting groups

Reporting group title	Cohort 1: Lapatinib 1500 mg
Reporting group description: Lapatinib 1500 milligrams (mg) administered orally once a day	
Reporting group title	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg
Reporting group description: Lapatinib 1000 mg and Pazopanib 400 mg administered orally once a day	
Reporting group title	Cohort 2: Lapatinib 1500 mg/Pazopanib 800 mg
Reporting group description: Lapatinib 1500 mg and Pazopanib 800 mg administered orally once a day	

Primary: Percentage of Participants with Progressive Disease at Week 12 in Cohort 1

End point title	Percentage of Participants with Progressive Disease at Week 12 in Cohort 1[1]

End point description:

The percentage of participants with progressive disease (PD) 12 weeks after randomization was measured. Per Response Evaluation Criteria In Solid Tumors (RECIST), a response of PD is defined as a >=20% increase in target lesions. Participants were also classified as having PD if their response at Week 12 was unknown or missing. Response was determined by an independent radiologist and by an investigator. Cohort 1: Modified Intent-to-Treat (ITT) Population (all randomized, centrally confirmed ErbB2 FISH-positive participants).

End point type	Primary

End point timeframe:

Week 12

Notes:

[1] - 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: The analysis of the endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Cohort 1: Lapatinib 1500 mg	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[2]	69[3]		
Units: percentage of participants				
number (not applicable)				
Independently Evaluated	38.9	36.2		
Investigator Evaluated	43.1	37.7		

Notes:

[2] - Cohort 1: Modified ITT Population

[3] - Cohort 1: Modified ITT Population

Statistical analyses

Statistical analysis title	Statisticial Analysis 1
Comparison groups	Cohort 1: Lapatinib 1500 mg v Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.3724
Method	Chi-squared
Parameter estimate	Percentage Difference
Point estimate	2.7
Confidence interval	
level	90 %
sides	2-sided
lower limit	-11
upper limit	16.3

Notes:

[4] - Difference in the percentage of independently-evaluated PD between lapatinib and combination therapy (lapatinib plus pazopanib)

Statistical analysis title	Statisticial Analysis 2
Comparison groups	Cohort 1: Lapatinib 1500 mg v Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.2578
Method	Chi-squared
Parameter estimate	Percentage Difference
Point estimate	5.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-8.4
upper limit	19.2

Notes:

[5] - Difference in the percentage of investigator-evaluated PD between lapatinib and combination therapy (lapatinib plus pazopanib)

Secondary: Overall Survival for Cohort 1

End point title	Overall Survival for Cohort 1[6]

End point description:

Overall survival (OS) is defined as the time from randomization until death due to any cause. Participants who are alive as of the date of last contact are censored. There was insufficient follow-up to adequately assess OS for Cohort 2. Median OS cannot be presented for the lapatinib arm because the upper bound of the 95% confidence interval is undefined due to insufficient follow-up.

End point type	Secondary

End point timeframe:

Randomization until death due to any cause (up to 106.43 weeks)

Notes:

[6] - 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: The analysis of the endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Cohort 1: Lapatinib 1500 mg	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	69[8]		
Units: weeks				
median (confidence interval 95%)	(to)	91 (69.4 to 91)		

Notes:

[7] - MITT Population

[8] - MITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Response at Week 12 for Cohort 1 and Cohort 2

End point title	Response at Week 12 for Cohort 1 and Cohort 2

End point description:

The percentage of participants achieving either a complete (CR) or partial (PR) tumor response per Response Evaluation Criteria in Solid Tumors (RECIST) is presented. CR, all detectable tumor has disappeared; PR, a >=30% decrease in the sum of the longest dimensions of the target lesions taking as a reference the baseline sum; Progressive disease (PD), a >=20% increase in target lesions; Stable Disease, small changes that do not meet previously given criteria. IRC, independent review committee. Participants with an unknown or missing response were treated as non-responders.

End point type	Secondary

End point timeframe:

Week 12

End point values	Cohort 1: Lapatinib 1500 mg	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg	Cohort 2: Lapatinib 1500 mg/Pazopanib 800 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72[9]	69[10]	36[11]	
Units: percentage of participants				
Complete response, IRC evaluated	0	0	0	
Complete response, Investigator evaluated	1	0	0	
Partial response, IRC evaluated	22	36	33	
Partial response, Investigator evaluated	26	45	50	
Stable disease, IRC evaluated	39	28	31	
Stable disease, Investigator evaluated	29	17	14	
Progressive disease, IRC evaluated	17	20	8	
Progressive disease, Investigator evaluated	38	20	11	
Unknown/missing, IRC evaluated	22	15	28	
Unknown/missing, Investigator	6	17	25	

Notes:

[9] - MITT Population

[10] - MITT Population

[11] - MITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response in Cohort 1

End point title	Duration of Response in Cohort 1[12]

End point description:

Duration of response is defined as the length of time from the time from the first observation of response until progression of disease or death. Duration of response depends on two things: (1) when response is counted as starting; (2) when response is counted as ending.There were insufficient data to adequately assess duration of response for Cohort 2. IRC, independent review committee. For participants who do not progress or die, duration of response was censored at the date of last adequate assessment.

End point type	Secondary

End point timeframe:

time from first documented evidence of complete or partial response until the first documented sign of disease progression or death due to any cause (up to 106.71 weeks)

Notes:

[12] - 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: The analysis of the endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Cohort 1: Lapatinib 1500 mg	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72[13]	69[14]		
Units: Weeks				
median (inter-quartile range (Q1-Q3))	27.1 (24.3 to 27.7)	24.3 (12.3 to 24.3)		

Notes:

[13] - MITT Population

[14] - MITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (Complete or Partial Response) in Cohort 1 and Cohort 2

End point title	Time to Response (Complete or Partial Response) in Cohort 1 and Cohort 2

End point description:

Time to response is defined as the time from randomization to the time of first documented evidence of a complete (CR) or partial response (PR). The time to response will depend on when the response is counted as starting. Per RECIST: CR, all detectable tumor has disappeared; PR, a >=30% decrease in the sum of the target dimensions of the target lesions taking as a reference the baseline sum.

End point type	Secondary

End point timeframe:

the time from randomization to the time of first documented evidence of complete or partial response (up to 81.14 weeks for Cohort 1 and 44.29 weeks for Cohort 2)

End point values	Cohort 1: Lapatinib 1500 mg	Cohort 1: Lapatinib 1000 mg/Pazopanib 400 mg	Cohort 2: Lapatinib 1500 mg/Pazopanib 800 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72[15]	69[16]	36[17]	
Units: Weeks				
median (confidence interval 95%)				
IRC evaluated	8.1 (7.9 to 11.4)	8.3 (8 to 11.9)	8.3 (7.4 to 8.7)	
Investigator Evaluated	8 (7.9 to 8.1)	8.1 (8 to 8.4)	8 (7.3 to 8.6)	

Notes:

[15] - MITT Population

[16] - MITT Population

[17] - MITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Progressive Disease at Week 12

End point title	Percentage of Participants with Progressive Disease at Week

End point description:

The percentage of participants with progressive disease (PD) 12 weeks after randomization was measured. Participants were classified as having PD if their response at Week 12 was unknown or missing. Per Response Evaluation Criteria In Solid Tumors (RECIST), PD is defined as a >=20% increase in target lesions. IRC, independent review committee.

End point type	Secondary

End point timeframe:

Week 12

Notes:

[18] - 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: The analysis of the endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Cohort 2: Lapatinib 1500 mg/Pazopanib 800 mg			
Subject group type	Reporting group			
Number of subjects analysed	36[19]			
Units: Percentage of participants				
PD+Missing+Unknown, IRC evaluated	36			
PD+Missing+Unknown, Investigator Evaluated	36			

Notes:

[19] - Cohort 2: MITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Study Entry until 28 days after the last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Cohort 1: Lapatinib 1500 mg
Reporting group description: Lapatinib 1500 milligrams (mg) administered orally once a day	
Reporting group title	Cohort 1 Lapatinib 1000 mg / Pazopanib 400 mg
Reporting group description: Lapatinib 1000 mg and Pazopanib 400 mg administered orally once a day	
Reporting group title	Cohort 2: Lapatinib 1500 mg / Pazopanib 800 mg
Reporting group description: Cohort 2: Lapatinib 1500 mg / Pazopanib 800 mg administered orally once a day	

Serious adverse events	Cohort 1: Lapatinib 1500 mg	Cohort 1 Lapatinib 1000 mg / Pazopanib 400 mg	Cohort 2: Lapatinib 1500 mg / Pazopanib 800 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 73 (13.70%)	18 / 76 (23.68%)	13 / 40 (32.50%)
number of deaths (all causes)	35	43	22
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 40 (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
Embolism			

subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	4 / 40 (10.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 40 (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
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 73 (2.74%)	1 / 76 (1.32%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Epistaxis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 40 (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
Pleural effusion			
subjects affected / exposed	1 / 73 (1.37%)	2 / 76 (2.63%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			

subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 40 (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			
Ejection fraction decreased			
subjects affected / exposed	0 / 73 (0.00%)	3 / 76 (3.95%)	2 / 40 (5.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alanine aminotransferase increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 40 (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
Upper limb fracture			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Left ventricular dysfunction			

subjects affected / exposed	0 / 73 (0.00%)	2 / 76 (2.63%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Somnolence			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 40 (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
Dizziness			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
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			
Anaemia			
subjects affected / exposed	0 / 73 (0.00%)	2 / 76 (2.63%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 73 (2.74%)	1 / 76 (1.32%)	3 / 40 (7.50%)
occurrences causally related to treatment / all	2 / 2	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 40 (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

Vomiting			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 40 (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
Abdominal pain upper			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 73 (1.37%)	1 / 76 (1.32%)	0 / 40 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 73 (4.11%)	0 / 76 (0.00%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	1 / 40 (2.50%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1: Lapatinib 1500 mg	Cohort 1 Lapatinib 1000 mg / Pazopanib 400 mg	Cohort 2: Lapatinib 1500 mg / Pazopanib 800 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 73 (86.30%)	71 / 76 (93.42%)	39 / 40 (97.50%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 73 (5.48%)	20 / 76 (26.32%)	15 / 40 (37.50%)
occurrences (all)	7	25	25
Hot flush			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 73 (12.33%)	9 / 76 (11.84%)	5 / 40 (12.50%)
occurrences (all)	13	11	5
Chest discomfort			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Chest pain			

subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	4 / 40 (10.00%)
occurrences (all)	0	0	4
Fatigue			
subjects affected / exposed	7 / 73 (9.59%)	12 / 76 (15.79%)	23 / 40 (57.50%)
occurrences (all)	7	18	25
Mucosal inflammation			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Pyrexia			
subjects affected / exposed	7 / 73 (9.59%)	6 / 76 (7.89%)	0 / 40 (0.00%)
occurrences (all)	10	7	0
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	4 / 40 (10.00%)
occurrences (all)	0	0	4
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 73 (6.85%)	7 / 76 (9.21%)	2 / 40 (5.00%)
occurrences (all)	5	8	3
Dysphonia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	4 / 73 (5.48%)	7 / 76 (9.21%)	13 / 40 (32.50%)
occurrences (all)	9	10	15
Oropharyngeal pain			
subjects affected / exposed	4 / 73 (5.48%)	5 / 76 (6.58%)	0 / 40 (0.00%)
occurrences (all)	4	5	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 73 (1.37%)	8 / 76 (10.53%)	5 / 40 (12.50%)
occurrences (all)	1	10	5
Depression			

subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	13 / 73 (17.81%)	25 / 76 (32.89%)	15 / 40 (37.50%)
occurrences (all)	21	39	20
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 73 (17.81%)	26 / 76 (34.21%)	15 / 40 (37.50%)
occurrences (all)	16	40	22
Blood bilirubin increased			
subjects affected / exposed	3 / 73 (4.11%)	10 / 76 (13.16%)	0 / 40 (0.00%)
occurrences (all)	4	17	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	7 / 40 (17.50%)
occurrences (all)	0	0	8
Platelet count decreased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	6
Crystal urine present			
subjects affected / exposed	0 / 73 (0.00%)	5 / 76 (6.58%)	0 / 40 (0.00%)
occurrences (all)	0	5	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 73 (0.00%)	4 / 76 (5.26%)	0 / 40 (0.00%)
occurrences (all)	0	5	0
Weight decreased			
subjects affected / exposed	3 / 73 (4.11%)	8 / 76 (10.53%)	5 / 40 (12.50%)
occurrences (all)	4	10	6
Ejection fraction decreased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 73 (13.70%)	9 / 76 (11.84%)	5 / 40 (12.50%)
occurrences (all)	10	9	6
Cardiac disorders			

Left ventricular dysfunction			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 73 (8.22%)	4 / 76 (5.26%)	7 / 40 (17.50%)
occurrences (all)	6	5	10
Dysgeusia			
subjects affected / exposed	1 / 73 (1.37%)	12 / 76 (15.79%)	12 / 40 (30.00%)
occurrences (all)	1	13	12
Headache			
subjects affected / exposed	7 / 73 (9.59%)	6 / 76 (7.89%)	11 / 40 (27.50%)
occurrences (all)	12	14	15
Neuropathy peripheral			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 73 (5.48%)	4 / 76 (5.26%)	0 / 40 (0.00%)
occurrences (all)	4	10	0
Leukopenia			
subjects affected / exposed	0 / 73 (0.00%)	6 / 76 (7.89%)	2 / 40 (5.00%)
occurrences (all)	0	8	10
Neutropenia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	5
Thrombocytopenia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	3

Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	8 / 73 (10.96%)	3 / 76 (3.95%)	0 / 40 (0.00%)
occurrences (all)	8	3	0
Abdominal discomfort			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	3
Abdominal pain			
subjects affected / exposed	3 / 73 (4.11%)	7 / 76 (9.21%)	11 / 40 (27.50%)
occurrences (all)	3	7	14
Abdominal pain upper			
subjects affected / exposed	2 / 73 (2.74%)	7 / 76 (9.21%)	3 / 40 (7.50%)
occurrences (all)	3	7	4
Constipation			
subjects affected / exposed	4 / 73 (5.48%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	4	0	2
Diarrhoea			
subjects affected / exposed	41 / 73 (56.16%)	52 / 76 (68.42%)	34 / 40 (85.00%)
occurrences (all)	81	172	86
Dry mouth			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Dyspepsia			
subjects affected / exposed	6 / 73 (8.22%)	8 / 76 (10.53%)	7 / 40 (17.50%)
occurrences (all)	9	10	8
Nausea			
subjects affected / exposed	13 / 73 (17.81%)	23 / 76 (30.26%)	28 / 40 (70.00%)
occurrences (all)	18	31	35
Rectal haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Stomatitis			
subjects affected / exposed	5 / 73 (6.85%)	5 / 76 (6.58%)	5 / 40 (12.50%)
occurrences (all)	6	22	7
Vomiting			

subjects affected / exposed	6 / 73 (8.22%)	15 / 76 (19.74%)	13 / 40 (32.50%)
occurrences (all)	10	28	19
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	7
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 73 (4.11%)	11 / 76 (14.47%)	10 / 40 (25.00%)
occurrences (all)	3	13	11
Dermatitis acneiform			
subjects affected / exposed	3 / 73 (4.11%)	5 / 76 (6.58%)	2 / 40 (5.00%)
occurrences (all)	4	5	3
Dry skin			
subjects affected / exposed	7 / 73 (9.59%)	5 / 76 (6.58%)	2 / 40 (5.00%)
occurrences (all)	7	5	2
Hair colour changes			
subjects affected / exposed	0 / 73 (0.00%)	14 / 76 (18.42%)	11 / 40 (27.50%)
occurrences (all)	0	14	13
Nail disorder			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	4
Pruritus			
subjects affected / exposed	10 / 73 (13.70%)	5 / 76 (6.58%)	4 / 40 (10.00%)
occurrences (all)	12	5	5
Rash			
subjects affected / exposed	21 / 73 (28.77%)	21 / 76 (27.63%)	16 / 40 (40.00%)
occurrences (all)	30	27	26
Rash macular			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Skin hypopigmentation			

subjects affected / exposed	0 / 73 (0.00%)	4 / 76 (5.26%)	0 / 40 (0.00%)
occurrences (all)	0	4	0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 40 (5.00%)
occurrences (all)	0	0	2
Proteinuria			
subjects affected / exposed	2 / 73 (2.74%)	8 / 76 (10.53%)	0 / 40 (0.00%)
occurrences (all)	2	12	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 73 (0.00%)	6 / 76 (7.89%)	0 / 40 (0.00%)
occurrences (all)	0	7	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	6 / 40 (15.00%)
occurrences (all)	0	0	8
Back pain			
subjects affected / exposed	5 / 73 (6.85%)	4 / 76 (5.26%)	5 / 40 (12.50%)
occurrences (all)	8	4	5
Musculoskeletal pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	4 / 40 (10.00%)
occurrences (all)	0	0	4
Myalgia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Neck pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	8 / 73 (10.96%)	9 / 76 (11.84%)	4 / 40 (10.00%)
occurrences (all)	9	13	6
Musculoskeletal chest pain			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	3
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	7 / 73 (9.59%)	4 / 76 (5.26%)	2 / 40 (5.00%)
occurrences (all)	8	6	2
Paronychia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	3 / 40 (7.50%)
occurrences (all)	0	0	4
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 73 (0.00%)	4 / 76 (5.26%)	0 / 40 (0.00%)
occurrences (all)	0	11	0
Hypokalaemia			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	4 / 40 (10.00%)
occurrences (all)	0	0	5
Decreased appetite			
subjects affected / exposed	10 / 73 (13.70%)	17 / 76 (22.37%)	14 / 40 (35.00%)
occurrences (all)	12	21	21

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2006	To correct omissions, include additional safety testing and make updates based on current clinical practice and recent experience.
23 April 2007	To add safety monitoring, interim analysis, evaluation of a higher combination dose regimen of lapatinib 1500 mg with pazapanib 800 mg.
19 June 2008	To update the safety information for lapatinib and pazopanib, modify the liver toxicity management guidelines, and add IDMC evaluation for safety.
28 October 2011	Study has met and reported primary and secondary objectives. Sites to discontinue collection of many assessments, whilst allowing 1 remaining subject to continue on treatment until unacceptable toxicity or disease progression. Collection of core safety data. Replace use of 100 & 500 mg tablets pazopanib with 200 & 400 mg tablets.

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.

In 2008 at primary completion, study was terminated. In 2011, protocol amendment 4 (Am4), allowed continuation of treatment until PD for the 1 par. This par. completed the study per Am 4. Par. last visit occurred, the study is considered completed.

Notes: