



## Clinical trial results:

### An open-label, single-arm, multicentre, Phase II study of oral lapatinib in combination with paclitaxel as first-line treatment for ErbB2-amplified metastatic breast cancer patients

#### Summary

EudraCT number	2005-003945-16
Trial protocol	LV
Global end of trial date	20 November 2013

#### Results information

Result version number	v1
This version publication date	16 March 2016
First version publication date	26 March 2015

#### Trial information

##### Trial identification

Sponsor protocol code	EGF105764
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##### 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	28 April 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 November 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate overall tumour response rate (ORR) of lapatinib combined with paclitaxel in patients with ErbB2-amplified metastatic breast cancer

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 May 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	Latvia: 5
Country: Number of subjects enrolled	Poland: 15
Country: Number of subjects enrolled	Russian Federation: 33
Country: Number of subjects enrolled	Romania: 4
Worldwide total number of subjects	57
EEA total number of subjects	24

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)	50
From 65 to 84 years	7
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Study medication was dispensed to the subject on Day 1 after it was confirmed that the participants met all eligibility criteria and all screening assessments were completed.

### Period 1

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

### Arms

Arm title	Lapatinib with paclitaxel
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Arm description:

Participants received lapatinib 1500 milligrams (mg) orally once daily (OD) with paclitaxel, administered as a 1-hour intravenous (IV) infusion at a dose of 80 mg/meters squared ( $m^2$ ) on Days 1, 8, and 15 ( $\pm 2$  days) of a 28-day treatment cycle for at least 6 months. Participants were treated until disease progression, unacceptable toxicity, or consent withdrawal.

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

Dosage and administration details:

1500mg, orally, OD

Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

80mg/m<sup>2</sup> ,IV weekly for 3 weeks in a 4 week cycle

Number of subjects in period 1	Lapatinib with paclitaxel
Started	57
Completed	8
Not completed	49
Consent withdrawn by subject	6
Participant Could Not Make a Checkup	1
Death	35
Study Is Terminating	3

Site Closed during Follow-up	2
Lost to follow-up	2

## Baseline characteristics

### Reporting groups

Reporting group title	Lapatinib with paclitaxel
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Reporting group description:

Participants received lapatinib 1500 milligrams (mg) orally once daily (OD) with paclitaxel, administered as a 1-hour intravenous (IV) infusion at a dose of 80 mg/meters squared ( $m^2$ ) on Days 1, 8, and 15 ( $\pm 2$  days) of a 28-day treatment cycle for at least 6 months. Participants were treated until disease progression, unacceptable toxicity, or consent withdrawal.

Reporting group values	Lapatinib with paclitaxel	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	52.3 $\pm 9.3$	-	
Gender categorical Units: Subjects			
Female	57	57	
Male	0	0	
Race Units: Subjects			
White - White/Caucasian/European Heritage	57	57	

## End points

### End points reporting groups

Reporting group title	Lapatinib with paclitaxel
Reporting group description:	
Participants received lapatinib 1500 milligrams (mg) orally once daily (OD) with paclitaxel, administered as a 1-hour intravenous (IV) infusion at a dose of 80 mg/meters squared (m <sup>2</sup> ) on Days 1, 8, and 15 (±2 days) of a 28-day treatment cycle for at least 6 months. Participants were treated until disease progression, unacceptable toxicity, or consent withdrawal.	

### Primary: Number of participants with a best overall response (OR) of confirmed complete response (CR) or partial response (PR), as assessed by the Independent Review Committee (IRC)

End point title	Number of participants with a best overall response (OR) of confirmed complete response (CR) or partial response (PR), as assessed by the Independent Review Committee (IRC) <sup>[1]</sup>
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#### End point description:

OR is defined as the number of participants achieving either a CR or PR, per Response Evaluation Criteria in Solid Tumors (RECIST). The best OR is defined as the best response recorded from the start of treatment until progressive disease (PD)/recurrence. CR is defined as the disappearance of all target lesions (TLs) and non-TLs. PR is defined as at least a 30% decrease in the sum of the longest diameters (LD) of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL(s), as assessed by the IRC. PD is defined as at least a 20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs. Responses were confirmed at subsequent assessments made ≥28 days after the original response. Participants with an unknown or missing response are treated as non-responders.

End point type	Primary
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#### End point timeframe:

From the first dose of study medication to the first documented evidence of a confirmed CR or PR (up to Week 86)

#### 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: The system does not allow for statistical analysis for studies with a single treatment arm.

End point values	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57 <sup>[2]</sup>			
Units: Participants				
CR	0			
PR	29			

#### Notes:

[2] - Intent-to-Treat (ITT) Population: all participants who received study medication.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with a best overall response (OR) of confirmed complete response (CR) or partial response (PR), as assessed by the Investigator

End point title	Number of participants with a best overall response (OR) of confirmed complete response (CR) or partial response (PR), as
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## End point description:

OR is defined as the number of participants achieving either a CR or PR, per RECIST. The best OR is defined as the best response recorded from the start of treatment until progressive disease (PD)/recurrence. CR is defined as the disappearance of all target lesions (TLs) and non-TLs. PR is defined as at least a 30% decrease in the sum of the longest diameters (LD) of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL(s), as assessed by the Investigator. PD is defined as at least a 20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs. Responses were confirmed at subsequent assessments made  $\geq 28$  days after the original response. Participants with an unknown or missing response are treated as non-responders.

End point type	Secondary
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## End point timeframe:

From the first dose of study medication to the first documented evidence of a confirmed CR or PR (up to Week 86)

End point values	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57 <sup>[3]</sup>			
Units: Participants				
CR	3			
PR	41			

Notes:

[3] - ITT Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of response (DoR), as assessed by the IRC

End point title	Duration of response (DoR), as assessed by the IRC
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## End point description:

DoR is defined for the subset of participants who had a confirmed CR (disappearance of all TLs and non-TLs) or PR ( $\geq 30\%$  decrease in the sum of the LD of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL[s]) as the time from the first documented evidence of a CR or PR until the first documentation of radiological PD or death due to breast cancer, if sooner. PD is defined as a  $\geq 20\%$  increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs. For participants who did not progress or die, DoR was censored on the date of the last radiological scan. If a participant had only a Baseline visit or did not have a date of a radiological scan that was later than the date of initiation of anti-cancer therapy, DoR was censored at the start date of treatment.

End point type	Secondary
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## End point timeframe:

From the first documented evidence of a PR or CR until the earlier of the date of disease progression or the date of death due to breast cancer (up to Week 86)

<b>End point values</b>	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	29 <sup>[4]</sup>			
Units: Weeks				
median (confidence interval 95%)	39.7 (26.9 to 50)			

Notes:

[4] - ITT Population. Only those participants with CR or PR were analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of response (DoR), as assessed by the Investigator

End point title	Duration of response (DoR), as assessed by the Investigator
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End point description:

DoR is defined for the subset of participants who had a confirmed CR (disappearance of all TLs and non-TLs) or PR ( $\geq 30\%$  decrease in the sum of the LD of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL[s]) as the time from the first documented evidence of a CR or PR until the first documentation of radiological PD or death due to breast cancer, if sooner. PD is defined as a  $\geq 20\%$  increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs. For participants who did not progress or die, DoR was censored on the date of the last radiological scan. If a participant had only a Baseline visit or did not have a date of a radiological scan that was later than the date of initiation of anti-cancer therapy, DoR was censored at the start date of treatment.

End point type	Secondary
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End point timeframe:

From the first documented evidence of a PR or CR until the earlier of the date of disease progression or the date of death due to breast cancer (up to Week 86)

<b>End point values</b>	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	44 <sup>[5]</sup>			
Units: Weeks				
median (confidence interval 95%)	42.3 (37.7 to 64.1)			

Notes:

[5] - ITT Population. Only those participants with CR or PR were analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to response, as assessed by the IRC

End point title	Time to response, as assessed by the IRC
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End point description:

Time to response is defined as the time from randomization until the first documented evidence of a PR or CR (whichever status is recorded first). Analysis was based on responses confirmed at a repeat assessment made at least 4 weeks after the initial response, with the time to response taken as the first time the response was observed, not the confirmation assessment. Participants who withdraw with no



tumor response were censored at the date of withdrawal from the study. CR is defined as the disappearance of all TLs and non-TLs. PR is defined as at least a 30% decrease in the sum of the LD of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL(s). PD is defined as at least a 20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs.

End point type	Secondary
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End point timeframe:

From randomization until the first documented evidence of a PR or CR (up to Week 86)

<b>End point values</b>	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	29 <sup>[6]</sup>			
Units: Weeks				
median (confidence interval 95%)	8.4 (7.9 to 11.1)			

Notes:

[6] - ITT Population. Only those participants with CR or PR were analyzed.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to response, as assessed by the Investigator

End point title	Time to response, as assessed by the Investigator
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End point description:

Time to response is defined as the time from randomization until the first documented evidence of a PR or CR (whichever status is recorded first). Analysis was based on responses confirmed at a repeat assessment made at least 4 weeks after the initial response, with the time to response taken as the first time the response was observed, not the confirmation assessment. Participants who withdraw with no tumor response were censored at the date of withdrawal from the study. CR is defined as the disappearance of all TLs and non-TLs. PR is defined as at least a 30% decrease in the sum of the LD of TLs, taking as a reference the Baseline sum LD and no PD, or complete resolution of TLs and the persistence of one or more non-TL(s). PD is defined as at least a 20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs.

End point type	Secondary
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End point timeframe:

From randomization until the first documented evidence of a PR or CR (up to Week 86)

<b>End point values</b>	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	44 <sup>[7]</sup>			
Units: Weeks				
median (confidence interval 95%)	8 (7.9 to 8.1)			

Notes:

[7] - ITT Population. Only those participants with CR or PR were analyzed.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time to progression, as assessed by the IRC and the Investigator

End point title	Time to progression, as assessed by the IRC and the Investigator
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End point description:

Time to progression is defined as the interval between the start date of treatment and the date of radiological disease progression or death due to breast cancer, whichever occurs first. Participants who did not progress or die were censored on the date of their last radiological assessment preceding the start of any additional anti-cancer therapy. PD is defined as at least a 20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs. Responses were confirmed at a subsequent assessment made no less than 28 days after the original response. Please note that the IRC upper limit of the 95% confidence interval could not be determined (not reached) because there were not enough events to be able to calculate; therefore the value of 99999 was entered which represents NA.

End point type	Secondary
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End point timeframe:

From the start date of treatment until the date of radiological disease progression or the date of death due to breast cancer (up to Week 86)

End point values	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57 <sup>[8]</sup>			
Units: Weeks				
median (confidence interval 95%)				
IRC	47.9 (40 to 99999)			
Investigator	50.9 (47 to 64.3)			

Notes:

[8] - ITT Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression-free survival, as assessed by the IRC and the Investigator

End point title	Progression-free survival, as assessed by the IRC and the Investigator
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End point description:

Progression-free survival is defined as the interval between the start date of treatment and the date of radiological disease progression or death due to any cause, whichever occurs first. Participants who did not progress in their disease were censored on the date of their last radiological assessment preceding the start of any additional anti-cancer therapy. PD is defined as at least a 20% increase in the sum of the LD of TLs, taking as a reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions or unequivocal progression of existing non-TLs. Responses were confirmed at a subsequent assessment made no less than 28 days after the original response. Please note that the IRC upper limit of the 95% confidence interval could not be determined (not reached) because there were not enough events to be able to calculate; therefore, the value of 99999 was entered which represents NA.

End point type	Secondary
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End point timeframe:

From the start date of treatment until the date of radiological disease progression or death due to any cause, whichever occurs first (up to Week 86)

<b>End point values</b>	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57 <sup>[9]</sup>			
Units: Weeks				
median (confidence interval 95%)				
IRC	47.9 (40 to 99999)			
Investigator	50.9 (47 to 64.3)			

Notes:

[9] - ITT Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall survival

End point title	Overall survival
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End point description:

Overall survival is defined as the interval between the date of treatment start and the date of death due to any cause. For participants who did not die, follow-up was censored as the date of last contact. For participants who did not die, follow-up was censored at the date of last contact. At the time of this analysis, the median and the 95% confidence interval could not be determined because there were not enough deaths to calculate these estimates; therefore, the value of 99999 was entered which represents NA.

End point type	Secondary
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End point timeframe:

From the date of the first dose until the date of death due to any cause (up to Week 86)

<b>End point values</b>	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57 <sup>[10]</sup>			
Units: Weeks				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[10] - ITT Population

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Number of participants with any adverse event (AE) or serious adverse event (SAE)**

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End point title	Number of participants with any adverse event (AE) or serious adverse event (SAE)
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End point description:

An AE is defined as any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, or is a congenital anomaly/birth defect. Medical or scientific judgment was exercised in deciding whether reporting was appropriate in other situations.

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End point type	Secondary
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End point timeframe:

From the start of study medication until 28 days after the last dose (up to Study Week 381)

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<b>End point values</b>	Lapatinib with paclitaxel			
Subject group type	Reporting group			
Number of subjects analysed	57 <sup>[11]</sup>			
Units: Participants				
Any AE	57			
Any SAE	11			

Notes:

[11] - ITT Population

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication until 28 days after the last dose (up to Study Week 381).

Adverse event reporting additional description:

SAEs and non-serious AEs are reported for members of the ITT Population, comprised of all participants who received study medication.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	Lapatinib plus paclitaxel
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Reporting group description:

Participants received lapatinib 1500 mg orally OD with paclitaxel, administered as a 1-hour IV infusion at a dose of 80 mg/m<sup>2</sup> on Days 1, 8, and 15 ( $\pm$ 2 days) of a 28-day treatment cycle for at least 6 months. Participants were treated until disease progression, unacceptable toxicity, or consent withdrawal.

Serious adverse events	Lapatinib plus paclitaxel		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 57 (19.30%)		
number of deaths (all causes)	35		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abscess soft tissue			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Lapatinib plus paclitaxel		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 57 (98.25%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 57 (17.54%)		
occurrences (all)	24		
Aspartate aminotransferase increased			

subjects affected / exposed	5 / 57 (8.77%)		
occurrences (all)	12		
Weight decreased			
subjects affected / exposed	4 / 57 (7.02%)		
occurrences (all)	7		
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	14 / 57 (24.56%)		
occurrences (all)	15		
Neuropathy peripheral			
subjects affected / exposed	8 / 57 (14.04%)		
occurrences (all)	8		
Dizziness			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	9		
Headache			
subjects affected / exposed	3 / 57 (5.26%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	25 / 57 (43.86%)		
occurrences (all)	70		
Leukopenia			
subjects affected / exposed	10 / 57 (17.54%)		
occurrences (all)	18		
Anaemia			
subjects affected / exposed	9 / 57 (15.79%)		
occurrences (all)	21		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 57 (26.32%)		
occurrences (all)	28		
Oedema peripheral			
subjects affected / exposed	6 / 57 (10.53%)		
occurrences (all)	9		
Asthenia			

subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 6		
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Abdominal pain upper subjects affected / exposed occurrences (all)  Nausea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	32 / 57 (56.14%) 143  9 / 57 (15.79%) 12  9 / 57 (15.79%) 11  6 / 57 (10.53%) 6		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Epistaxis subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 5  4 / 57 (7.02%) 5		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 4		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)  Alopecia	23 / 57 (40.35%) 39		



subjects affected / exposed occurrences (all)	9 / 57 (15.79%) 17		
Nail disorder subjects affected / exposed occurrences (all)	6 / 57 (10.53%) 11		
Nail dystrophy subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 5		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	6 / 57 (10.53%) 13		
Bone pain subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 5		
Infections and infestations			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 57 (10.53%) 6		
Erysipelas subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 5		
Paronychia subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 7		
Respiratory tract infection subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 4		
Metabolism and nutrition disorders			
Hypokalaemia subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 17		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2007	Amendment 1/ to allow use of generic paclitaxel
13 June 2008	Amendment 2/ The protocol has been amended to include the information regarding hepatotoxicity associated with lapatinib treatment.
14 July 2008	Amendment 2/ As part of the liver toxicity update of GM2005/00370/02, inclusion of pharmacokinetics sample needing to be taken has been added to the follow up criteria in section 6.2.3.2.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported