Clinical trial results:
LUX-Breast 2: An open-label, multinational, phase-II trial of Afatinib (BIBW 2992) in patients with metastatic human epidermal growth factor receptor (HER2) - overexpressing breast cancer failing HER2 - targeted treatment in the neoadjuvant and/or adjuvant treatment setting

Summary

EudraCT number	2010-021945-29
Trial protocol	GB
Global end of trial date	13 March 2017

Results information

Result version number	v1
This version publication date	24 March 2018
First version publication date	24 March 2018

Trial information

Trial identification

Sponsor protocol code	1200.98

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01271725
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	10 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2017
Global end of trial reached?	Yes
Global end of trial date	13 March 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy and safety of afatinib alone, and of afatinib in combination with weekly paclitaxel or vinorelbine upon progression on afatinib monotherapy, in patients with HER2-overexpressing, metastatic breast cancer, who failed HER2-targeted treatment in the adjuvant and/or neoadjuvant setting.

Protection of trial subjects:

All patients were informed that they were free to withdraw their consent at any time during the study without penalty or prejudice. The patients were informed that their personal trial related data would be considered confidential and used by BI in accordance with the local data protection laws. The level of disclosure was explained to the patients. The patients were also informed that their medical records could be examined by Clinical Quality Assurance auditors appointed by BI, by members of the appropriate IEC/IRB, and by inspectors from regulatory authorities. Confidentiality of patient data was ensured by the use of depersonalised patient identification codes (patient numbers). The terms and conditions of the insurance cover were available to the investigator and the patients in the Investigator Site File.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 July 2011
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	Hong Kong: 4
Country: Number of subjects enrolled	India: 19
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Taiwan: 32
Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	87
EEA total number of subjects	9

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	77
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

An open-label, multinational, phase-II trial of Afatinib (BIBW 2992) in patients with metastatic human epidermal growth factor receptor (HER2) - overexpressing breast cancer failing HER2 - targeted treatment in the neoadjuvant and/or adjuvant treatment setting

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended a specialist sites which ensured that they met all strictly implemented inclusion/exclusion criteria. Subjects were not to be entered to trial treatment if any one of the specific entry criteria was violated.

Period 1

Period 1 title	Part A
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

An open-label trial

Arms

Arm title	Afatinib monotherapy

Arm description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) filmcoated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal. A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated.

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) film coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal

Number of subjects in period 1[1]	Afatinib monotherapy
Started	74
Completed	39
Not completed	35
Adverse event, serious fatal	3
Consent withdrawn by subject	12
Adverse event, non-fatal	5
Other than specified	3
Clinical signs/symptoms of progression	2

Lost to follow-up	1
Progressive disease according to RECIST	8
Protocol deviation	1

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: Baseline characteristics are based on the patients who were successfully completed the screening period and received at least one of the trial medication.

Period 2

Period 2 title	Part B
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

An open-label trial

Arms

Arm title	Afatinib and Paclitaxel or Vinorelbine combination therapy

Arm description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 80 mg/square meter (m2) Paclitaxel concentrate for intravenous infusion or 25 mg/m2 Vinorelbine concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

Arm type	Experimental
Investigational medicinal product name	Afatinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) film coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal

Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patient received 25 mg/m2 Vinorelbine concentrate for intravenous infusion once weekly.

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

Dosage and administration details:

Patient received 80 mg/square meter (m2) Paclitaxel concentrate for intravenous infusion once weekly.

Number of subjects in period 2	Afatinib and Paclitaxel or Vinorelbine combination therapy
Started	39
Completed	27
Not completed	12
Consent withdrawn by subject	6
Adverse event, non-fatal	1
Other than specified	2
Clinical signs/symptoms of progression	2
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib monotherapy
Reporting group description:	
Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) filmcoated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal. A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated.	

Reporting group values	Afatinib monotherapy	Total	
Number of subjects	74	74	
Age categorical			
The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine.			
Units: Subjects			
Age Continuous			
Age at the time of signing informed consent form is presented. The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine. The baseline population analysis set was Treated set.			
Units: years			
arithmetic mean	51.3		
standard deviation	± 10.6	-	
Sex: Female, Male			
Number of subjects is categorized as Male or Female. The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine.			
Units: Subjects			
Female	74	74	
Male	0	0	
Race (NIH/OMB)			
Ethnicity was not captured in this trial. The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	47	47	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	27	27	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Afatinib monotherapy

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) filmcoated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal. A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated.

Reporting group title	Afatinib and Paclitaxel or Vinorelbine combination therapy

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 80 mg/square meter (m2) Paclitaxel concentrate for intravenous infusion or 25 mg/m2 Vinorelbine concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

Subject analysis set title	Afatinib and Vinorelbine combination therapy
Subject analysis set type	Full analysis

Subject analysis set description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 25 mg/m2 Vinorelbine concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

Subject analysis set title	Afatinib and Paclitaxel combination therapy
Subject analysis set type	Full analysis

Subject analysis set description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 80 mg/square meter (m2) Paclitaxel concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

Primary: Objective Response (OR) assessed by Response Evaluation Criteria in Solid Tumours Version (RECIST) 1.1

End point title	Objective Response (OR) assessed by Response Evaluation Criteria in Solid Tumours Version (RECIST) 1.1[1]

End point description:

Objective response according to RECIST v1.1. Best overall response of confirmed complete response (CR) or confirmed partial response (PR) recorded since first administration of trial medication and until the earliest of disease progression, death or start of next treatment in each part separately. Percentage of participants with OR along with exact 95% Confidence Interval by Clopper and Pearson is presented. The treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. The treated set for combination therapy comprised all patients who received at least 1 dose of each of afatinib and paclitaxel, or of afatinib and vinorelbine.

End point type	Primary

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis test was tested.

End point values	Afatinib monotherapy	Afatinib and Paclitaxel or Vinorelbine combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[2]	39[3]		
Units: Percentage				
number (confidence interval 95%)	18 (10 to 28)	31 (17 to 48)		

Notes:

[2] - Treated Set

[3] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response According to RECIST v1.1 (With confirmation)

End point title	Best Overall Response According to RECIST v1.1 (With confirmation)

End point description:

Best overall response is the best overall response to trial medication according to RECIST version 1.1 and was calculated relative to the baseline of each respective part. Percentage of participants with best overall response along with exact 95% Confidence Interval by Clopper and Pearson is presented. Best overall response was defined as the best response recorded at any time from the first administration of drug to the End of Treatment (EOT). As Per RECIST v1.1 for target lesions and assessed by Magnetic resonance imaging (MRI): Complete Response (CR), disappearance of all target lesions; Partial Response (PR) & gt;=30% decrease in the sum of the longest diameter of target lesions; progression, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression.

End point type	Secondary

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

End point values	Afatinib monotherapy	Afatinib and Paclitaxel or Vinorelbine combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[4]	39[5]		
Units: Percentage				
number (confidence interval 95%)				
Complete response (CR)|	1 (0 to 7)	0 (0 to 9)		
Partial response (PR)|	16 (9 to 27)	31 (17 to 48)		
Stable disease (SD)|	45 (33 to 57)	46 (30 to 63)		
Progressive disease|	28 (19 to 40)	10 (3 to 24)		
Not evaluable|	9 (4 to 19)	13 (4 to 27)		

Notes:

[4] - Treated set

[5] - Treated set

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response According to RECIST v1.1 (Regardless of confirmation)

End point title	Best Overall Response According to RECIST v1.1 (Regardless of confirmation)

End point description:

Best overall response is the best overall response to trial medication (without clinical disease assessment) according to RECIST version 1.1 and was calculated relative to the baseline of each respective part. Percentage of participants with best overall response along with exact 95% Confidence Interval by Clopper and Pearson is presented. Best overall response was defined as the best response recorded at any time from the first administration of drug to the End of Treatment (EOT). As Per RECIST v1.1 for target lesions and assessed by MRI: Complete Response (CR), disappearance of all target lesions; Partial Response (PR) & gt;=30% decrease in the sum of the longest diameter of target lesions; progression, as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for disease progression.

End point type	Secondary

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

End point values	Afatinib monotherapy	Afatinib and Paclitaxel or Vinorelbine combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[6]	39[7]		
Units: Percentage				
number (confidence interval 95%)				
Complete response (CR)|	1 (0 to 7)	0 (0 to 9)		
Partial response (PR)|	19 (11 to 30)	44 (28 to 60)		
Stable disease (SD)|	42 (31 to 54)	33 (19 to 50)		
Progressive disease|	28 (19 to 40)	10 (3 to 24)		
Not evaluable|	9 (4 to 19)	13 (4 to 27)		

Notes:

[6] - Treated Set

[7] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression Free Survival is defined as the time from the drug start date to the date of 1st disease progression or death for monotherapy and 2nd disease progression or death from the drug start date of the combination therapy for combination therapy'. Median is calculated from the Kaplan−Meier curve.

End point type	Secondary

End point timeframe:

From drug start date in monotherapy to 1st disease progression and drug start date in combination therapy to 2nd disease progression

End point values	Afatinib monotherapy	Afatinib and Paclitaxel or Vinorelbine combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[8]	39[9]		
Units: Days				
median (confidence interval 95%)	86.0 (72.0 to 127.0)	135.0 (95.0 to 224.0)		

Notes:

[8] - Treated Set

[9] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response according to RECIST v1.1

End point title	Duration of Objective Response according to RECIST v1.1

End point description:

Duration of objective response, defined as the time from first objective response to the time of progression or death. (regardless of confirmation)

End point type	Secondary

End point timeframe:

From the first objective response to the time of progression or death

End point values	Afatinib monotherapy	Afatinib and Paclitaxel or Vinorelbine combination therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74[10]	39[11]		
Units: Days				
median (confidence interval 95%)	168.5 (85.0 to 253.0)	125.0 (73.0 to 505.0)		

Notes:

[10] - Treated Set

[11] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients with highest common terminology criteria for adverse events (CTCAE) version 3.0 Grade of 3 or higher

End point title	Percentage of patients with highest common terminology criteria for adverse events (CTCAE) version 3.0 Grade of 3 or

	higher

End point description:

Percentage of patients with highest common terminology criteria for adverse events (CTCAE) version 3.0 Grade of 3 or higher.

End point type	Secondary

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

End point values	Afatinib monotherapy	Afatinib and Vinorelbine combination therapy	Afatinib and Paclitaxel combination therapy	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	74[12]	13[13]	26[14]	
Units: Percentage	43	62	65	

Notes:

[12] - Treated Set

[13] - Treated Set

[14] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in systolic blood pressure (SBP)

End point title	Change from baseline to end of treatment in systolic blood pressure (SBP)

End point description:

Change from baseline to end of treatment in systolic blood pressure (SBP).

End point type	Secondary

End point timeframe:

Baseline and End of treatment period

End point values	Afatinib monotherapy	Afatinib and Vinorelbine combination therapy	Afatinib and Paclitaxel combination therapy	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	74[15]	13[16]	26[17]	
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)	-1.2 (± 17.9)	-1.0 (± 15.1)	-3.7 (± 12.1)	

Notes:

[15] - Treated Set

[16] - Treated Set

[17] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to end of treatment in diastolic blood pressure (DBP)

End point title	Change from baseline to end of treatment in diastolic blood pressure (DBP)

End point description:

Change from baseline to end of treatment in diastolic blood pressure (DBP).

End point type	Secondary

End point timeframe:

Baseline and End of treatment period

End point values	Afatinib monotherapy	Afatinib and Vinorelbine combination therapy	Afatinib and Paclitaxel combination therapy	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	74[18]	13[19]	26[20]	
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)	-1.8 (± 12.0)	1.9 (± 10.7)	-1.6 (± 10.0)	

Notes:

[18] - Treated Set

[19] - Treated Set

[20] - Treated Set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of patient with possibly clinically significant (PCS) laboratory values

End point title	Number of patient with possibly clinically significant (PCS) laboratory values

End point description:

Number of patient with possibly clinically significant (PCS) laboratory values by functional group (haematology, differentials, coagulation, electrolytes, enzymes, and substrates). These findings were reported as adverse events.
99999: Not Applicable

End point type	Secondary

End point timeframe:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

End point values	Afatinib monotherapy	Afatinib and Vinorelbine combination therapy	Afatinib and Paclitaxel combination therapy	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	74[21]	13[22]	26[23]	
Units: Number of Participants				

Weight decreased|	10	1	4	
Alanine aminotransferase increased|	5	0	4	
Neutrophil count decreased|	99999	2	1	
Aspartate aminotransferase increased|	3	1	3	
Alanine aminotransferase|	99999	1	0	
Aspartate aminotransferase|	99999	1	0	
Blood creatinine increased|	2	0	2	
Blood glucose decreased|	99999	1	0	
Blood lactate dehydrogenase increased|	2	0	2	
Blood uric acid increased|	2	0	2	
Blood calcium decreased|	99999	0	1	
Blood sodium decreased|	1	0	1	
Haemoglobin decreased|	3	0	1	
Urine output decreased|	99999	0	1	
White blood cell count decreased|	1	0	1	
Blood alkaline phosphatase increased|	4	99999	99999	
Blood alkaline phosphatase|	1	99999	99999	
Blood creatine phosphokinase increased|	1	99999	99999	
Blood lactic acid increased|	1	99999	99999	
Blood potassium decreased|	1	99999	99999	
Glomerular filtration rate decreased|	1	99999	99999	
Liver function test increased|	1	99999	99999	
Lymphocyte count decreased|	1	99999	99999	
Platelet count decreased|	1	99999	99999	
Red blood cell sedimentation rate increased|	1	99999	99999	

Notes:

[21] - Treated Set

[22] - Treated Set

[23] - Treated Set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the initial dose of study drug until 28 days after end of the treatment period, up to 1562 days

Adverse event reporting additional description:

Safety analyses were performed for monotherapy and combination therapy separately using the respective treated sets. Treated set for monotherapy comprised all patients who received at least 1 dose of afatinib. Treated set for combination therapy comprised all patients who received at least 1 dose of each afatinib/paclitaxel or afatinib/vinorelbine.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Afatinib monotherapy

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 milligram (mg) film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal. A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated.

Reporting group title	Afatinib and Vinorelbine combination therapy

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 25 mg/m2 Vinorelbine concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

Reporting group title	Afatinib and Paclitaxel combination therapy

Reporting group description:

Patient received Afatinib monotherapy orally once daily at a dose of 40 mg film-coated tablets until progression of their disease, unacceptable adverse events or other reason necessitating withdrawal (A dose reduction to 30mg and 20mg was possible if 40mg was not tolerated) and 80 mg/square meter (m2) Paclitaxel concentrate for intravenous infusion once weekly starting after treatment failure on afatinib monotherapy

Serious adverse events	Afatinib monotherapy	Afatinib and Vinorelbine combination therapy	Afatinib and Paclitaxel combination therapy
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 74 (24.32%)	5 / 13 (38.46%)	10 / 26 (38.46%)
number of deaths (all causes)	6	1	5
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer metastatic			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Malignant neoplasm progression			

subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Metastases to central nervous system			
subjects affected / exposed	2 / 74 (2.70%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Neoplasm progression			
subjects affected / exposed	4 / 74 (5.41%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 1
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 74 (4.05%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (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
Pyrexia			
subjects affected / exposed	0 / 74 (0.00%)	2 / 13 (15.38%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	3 / 74 (4.05%)	2 / 13 (15.38%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (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
Respiratory distress			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Product issues			
Device leakage			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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

Device occlusion			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuralgia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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
Seizure			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (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
Febrile neutropenia			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 74 (2.70%)	2 / 13 (15.38%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 4	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	3 / 74 (4.05%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	2 / 4	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 74 (2.70%)	1 / 13 (7.69%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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
Renal and urinary disorders			
Azotaemia			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal failure			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	1 / 26 (3.85%)
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			
Diarrhoea infectious			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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
Herpes zoster			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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
Liver abscess			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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

Upper respiratory tract infection			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (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
Urinary tract infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 74 (2.70%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
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	Afatinib monotherapy	Afatinib and Vinorelbine combination therapy	Afatinib and Paclitaxel combination therapy
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 74 (90.54%)	13 / 13 (100.00%)	23 / 26 (88.46%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	6 / 74 (8.11%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences (all)	6	0	1
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 74 (0.00%)	2 / 13 (15.38%)	0 / 26 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	5 / 74 (6.76%)	2 / 13 (15.38%)	7 / 26 (26.92%)
occurrences (all)	5	8	8
Fatigue			
subjects affected / exposed	7 / 74 (9.46%)	0 / 13 (0.00%)	5 / 26 (19.23%)
occurrences (all)	7	0	5
Mucosal inflammation			
subjects affected / exposed	15 / 74 (20.27%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences (all)	22	0	2
Oedema			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	2
Pain			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Pyrexia			
subjects affected / exposed	4 / 74 (5.41%)	1 / 13 (7.69%)	2 / 26 (7.69%)
occurrences (all)	5	2	2
Ulcer			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 74 (10.81%)	0 / 13 (0.00%)	3 / 26 (11.54%)
occurrences (all)	8	0	4
Dyspnoea			
subjects affected / exposed	8 / 74 (10.81%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	8	0	2
Epistaxis			
subjects affected / exposed	6 / 74 (8.11%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	6	0	2
Oropharyngeal pain			

subjects affected / exposed	3 / 74 (4.05%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	3	0	2
Rhinorrhoea			
subjects affected / exposed	4 / 74 (5.41%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences (all)	5	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	3 / 26 (11.54%)
occurrences (all)	1	0	3
Investigations			
Alanine aminotransferase			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Alanine aminotransferase increased			
subjects affected / exposed	5 / 74 (6.76%)	0 / 13 (0.00%)	4 / 26 (15.38%)
occurrences (all)	5	0	6
Aspartate aminotransferase			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 74 (4.05%)	1 / 13 (7.69%)	3 / 26 (11.54%)
occurrences (all)	3	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 74 (5.41%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences (all)	4	0	0
Blood glucose decreased			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 74 (2.70%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	2	0	2
Blood uric acid increased			
subjects affected / exposed	2 / 74 (2.70%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	3	0	2
Neutrophil count decreased			

subjects affected / exposed	0 / 74 (0.00%)	2 / 13 (15.38%)	1 / 26 (3.85%)
occurrences (all)	0	3	1
Weight decreased			
subjects affected / exposed	10 / 74 (13.51%)	1 / 13 (7.69%)	4 / 26 (15.38%)
occurrences (all)	11	1	5
Injury, poisoning and procedural complications			
Wound			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Wound secretion			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 74 (4.05%)	1 / 13 (7.69%)	1 / 26 (3.85%)
occurrences (all)	3	1	1
Headache			
subjects affected / exposed	7 / 74 (9.46%)	1 / 13 (7.69%)	2 / 26 (7.69%)
occurrences (all)	8	1	5
Hypoaesthesia			
subjects affected / exposed	3 / 74 (4.05%)	1 / 13 (7.69%)	3 / 26 (11.54%)
occurrences (all)	3	1	3
Neuropathy peripheral			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	4 / 26 (15.38%)
occurrences (all)	0	0	5
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 74 (9.46%)	4 / 13 (30.77%)	13 / 26 (50.00%)
occurrences (all)	7	4	17
Leukopenia			
subjects affected / exposed	1 / 74 (1.35%)	4 / 13 (30.77%)	5 / 26 (19.23%)
occurrences (all)	2	7	7
Neutropenia			

subjects affected / exposed	1 / 74 (1.35%)	9 / 13 (69.23%)	9 / 26 (34.62%)
occurrences (all)	1	24	36
Thrombocytopenia			
subjects affected / exposed	2 / 74 (2.70%)	1 / 13 (7.69%)	1 / 26 (3.85%)
occurrences (all)	3	3	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	2
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 74 (4.05%)	1 / 13 (7.69%)	1 / 26 (3.85%)
occurrences (all)	3	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 74 (6.76%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences (all)	5	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	3 / 26 (11.54%)
occurrences (all)	1	0	3
Anal inflammation			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	3 / 26 (11.54%)
occurrences (all)	0	0	3
Diarrhoea			
subjects affected / exposed	50 / 74 (67.57%)	3 / 13 (23.08%)	9 / 26 (34.62%)
occurrences (all)	101	4	18
Haemorrhoids			
subjects affected / exposed	3 / 74 (4.05%)	1 / 13 (7.69%)	2 / 26 (7.69%)
occurrences (all)	3	1	2
Mouth ulceration			
subjects affected / exposed	8 / 74 (10.81%)	2 / 13 (15.38%)	2 / 26 (7.69%)
occurrences (all)	8	2	2
Nausea			

subjects affected / exposed	9 / 74 (12.16%)	1 / 13 (7.69%)	4 / 26 (15.38%)
occurrences (all)	9	1	13
Stomatitis			
subjects affected / exposed	3 / 74 (4.05%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	4	1	0
Vomiting			
subjects affected / exposed	6 / 74 (8.11%)	2 / 13 (15.38%)	4 / 26 (15.38%)
occurrences (all)	6	2	5
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 74 (6.76%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences (all)	6	0	0
Alopecia			
subjects affected / exposed	2 / 74 (2.70%)	1 / 13 (7.69%)	10 / 26 (38.46%)
occurrences (all)	2	1	10
Dermatitis			
subjects affected / exposed	5 / 74 (6.76%)	2 / 13 (15.38%)	1 / 26 (3.85%)
occurrences (all)	5	2	1
Eczema			
subjects affected / exposed	4 / 74 (5.41%)	1 / 13 (7.69%)	1 / 26 (3.85%)
occurrences (all)	5	2	1
Eczema asteatotic			
subjects affected / exposed	1 / 74 (1.35%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	1	1	0
Nail bed inflammation			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	13 / 74 (17.57%)	1 / 13 (7.69%)	3 / 26 (11.54%)
occurrences (all)	15	1	3
Pruritus			
subjects affected / exposed	5 / 74 (6.76%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	6	0	2
Rash			

subjects affected / exposed	37 / 74 (50.00%)	3 / 13 (23.08%)	4 / 26 (15.38%)
occurrences (all)	42	4	8
Rash pruritic			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	2 / 26 (7.69%)
occurrences (all)	0	2	2
Skin hyperpigmentation			
subjects affected / exposed	2 / 74 (2.70%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	2	0	2
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	2	0	3
Back pain			
subjects affected / exposed	2 / 74 (2.70%)	2 / 13 (15.38%)	0 / 26 (0.00%)
occurrences (all)	3	2	0
Musculoskeletal pain			
subjects affected / exposed	5 / 74 (6.76%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences (all)	5	0	1
Pain in extremity			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	1 / 26 (3.85%)
occurrences (all)	0	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	4 / 74 (5.41%)	0 / 13 (0.00%)	0 / 26 (0.00%)
occurrences (all)	5	0	0
Gastroenteritis			

subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 74 (1.35%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	1	0	3
Paronychia			
subjects affected / exposed	9 / 74 (12.16%)	2 / 13 (15.38%)	1 / 26 (3.85%)
occurrences (all)	12	2	6
Periodontitis			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Pulpitis dental			
subjects affected / exposed	0 / 74 (0.00%)	1 / 13 (7.69%)	0 / 26 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	4
Upper respiratory tract infection			
subjects affected / exposed	4 / 74 (5.41%)	0 / 13 (0.00%)	1 / 26 (3.85%)
occurrences (all)	4	0	3
Urinary tract infection			
subjects affected / exposed	3 / 74 (4.05%)	0 / 13 (0.00%)	3 / 26 (11.54%)
occurrences (all)	3	0	4
Viral infection			
subjects affected / exposed	0 / 74 (0.00%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 74 (6.76%)	0 / 13 (0.00%)	4 / 26 (15.38%)
occurrences (all)	5	0	4
Hypocalcaemia			
subjects affected / exposed	2 / 74 (2.70%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	2	0	3
Hypokalaemia			
subjects affected / exposed	3 / 74 (4.05%)	0 / 13 (0.00%)	2 / 26 (7.69%)
occurrences (all)	6	0	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2010	The schedule for tumour assessments was clarified. Use of contraception post study for each of the trial medications was defined, at the request of the Competent Authorities and to align the text with the summaries of product characteristics (SmPCs) for paclitaxel and vinorelbine. Vinorelbine infusion time was clarified. An explanation was added regarding handling of hospitalisations for administrative reasons.
27 April 2011	It was clarified that haematology (complete blood count) results were required prior to chemotherapy. Guidance on the use of radiotherapy during the trial was added. Palliative radiotherapy became allowed. An exclusion criterion was amended to allow palliative radiotherapy. Guidance on the timing of study medication intake was corrected. The requirement for a platelet count value before treatment with paclitaxel was added. The adverse event reporting periods were corrected. It was clarified that the reference SmPC was not the local version.
29 July 2011	'LUX-Breast 2' was added to the title to indicate that this trial is part of the LUX-breast program
06 December 2011	Text was added regarding drug-induced liver injury (DILI) in line with new corporate standards. An exclusion criterion was added to clarify that the intention was to include patients who required first-line treatment for metastatic breast cancer. Guidance on missed doses was added. Text was added regarding AE that are considered 'always serious' in line with new corporate standards.
06 November 2012	Timing of ECHO and MUGA scans during combination therapy was added and clarified. Guidance on the concomitant use of P-gp inhibitors and inducers- was updated, and a list medications in this class was added. Information about the incidence of keratitis in licensed epidermal growth factor receptor (EGFR) inhibitors was added. The requirement for a platelet count to be available prior to the start of each vinorelbine infusion was added, a statement on vinorelbine dose adjustment for severe hepatic impairment was added, and instructions for diluting vinorelbine were amended following the release of an updated SmPC for vinorelbine. The name of the manufacturer of paclitaxel was removed following a shortage of paclitaxel from Hospira United Kingdom. Reporting of worsening of underlying disease or other pre-existing conditions, change in vital signs, Electrocardiogram, physical examination and laboratory test results were modified for alignment with project standard definitions.
27 June 2013	The inclusion of patients after progression on Afatinib monotherapy (part A) into the afatinib + vinorelbine combination in Part B was stopped. Patients in part A could only go into the Afatinib + Paclitaxel arm. Enrolment of new patients into the trial was also stopped. The description of bottles of afatinib was removed in case future supplies were switched to the marketed product

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.

Enrollment of patients into the afatinib and vinorelbine combination option was stopped prematurely following a benefit-risk analysis in other trial. Any patients who were already benefiting from this combination were allowed to continue.

Notes: