Clinical trial results:
An open label, phase II trial of Afatinib with or without Vinorelbine for the treatment of HER2-overexpressing inflammatory breast cancer.

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2010-024454-10
Trial protocol	GB
Global end of trial date	18 November 2014

Results information

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

Trial information

Trial identification

Sponsor protocol code	1200.89

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01325428
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 Pharma GmbH & Co. KG, +1 +1 800 243 0127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim Pharma GmbH & Co. KG, +1 +1 800 243 0127, 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	16 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2014
Global end of trial reached?	Yes
Global end of trial date	18 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objectives were to investigate the efficacy and safety of Afatinib alone and Afatinib in combination with weekly Vinorelbine upon progression on Afatinib monotherapy in patients with HER2-overexpressing inflammatory breast cancer (IBC).

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented whereby doses would be reduced if required. In case of treatment-related AEs, the 40 mg dose could be reduced by increments of 10 mg to 30 mg once daily or 20 mg once daily. Thereafter, if further events were reported which required dose reductions, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 December 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	Australia: 2
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Thailand: 12
Country: Number of subjects enrolled	Tunisia: 2
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	29
EEA total number of subjects	5

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	27
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open-label single arm study conducted in two sequential parts (Part A in which patients were treated with Afatinib (BIBW 2992) as Monotherapy; Part B in which patients were treated with Afatinib plus Vinorelbine as combination therapy). Patients continued from Part A to Part B upon progression of disease in Part A.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (the subjects) met all strictly implemented inclusion/exclusion criteria. Subjects were not allocated to trial treatment if any one of the specific entry criteria were violated.

Period 1

Period 1 title	Part A: Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part A: Afatinib Once Daily (OD).

Arm description:

Part A: Patients received Afatinib tablets, 40 mg taken orally Once Daily (OD) until Progression of their Disease (PD). In case of treatment-related adverse events (AEs), the 40 mg dose could be reduced by increments of 10 mg to 30 mg once daily or 20 mg once daily. Patients were treated until PD in Part A, then they could continue with Afatinib and Vinorelbine in Part B.

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:

Patients received Afatinib tablets, 40 mg taken orally Once Daily (OD).

Number of subjects in period 1[1]	Part A: Afatinib Once Daily (OD).
Started	26
Completed	10
Not completed	16
Other reason not defined above	2
Refused continue taking trial medication	2
Clinical signs, symptoms of progression	2
Other adverse event	1
Progressive disease according to RECIST	9

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 patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Period 2

Period 2 title	Part B: Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part B: Afatinib+V (Vinorelbine).

Arm description:

Part B: Upon first Progression of Disease (PD), patients could enter Part B of the study, during which they continued to be treated with Afatinib at the previously applied dose in Part A and additionally were treated with Vinorelbine 25 mg/m2 per week via intravenous (i.v) infusion. Patients treated with Afatinib and Vinorelbine combination therapy could continue to receive treatment until second progression of disease, intolerable side effects, or withdrawal of consent. A patient was deemed to have completed the trial once they showed progressive disease according to RECIST (1.1) in Part B.

Arm type	Experimental
Investigational medicinal product name	Vinorelbine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Vinorelbine was administered as 25 mg/m2 per week via intravenous (i.v) infusion.

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:

Patients received Afatinib tablets, 40 mg taken orally Once Daily (OD).

Number of subjects in period 2	Part B: Afatinib+V (Vinorelbine).
Started	10
Completed	7
Not completed	3
Refused continue taking trial medication	2
Other reason not defined above	1

Baseline characteristics

Reporting groups

Reporting group title	Part A: Treatment Period

Reporting group description:

Part A: Patients received Afatinib tablets, 40 mg taken orally Once Daily (OD) until Progression of their Disease (PD). In case of treatment-related AEs, the 40 mg dose could be reduced by increments of 10 mg to 30 mg once daily or 20 mg once daily.

Reporting group values	Part A: Treatment Period	Total	
Number of subjects	26	26	
Age categorical Units: Subjects			

Age continuous			
TRT A Treated set - TS (Part A): All patients who were documented to have taken at least one dose of Afatinib in Part A. TRT B Treated set (Part B): All patients who received at least one dose each of Afatinib and Vinorelbine in Part B.			
Units: years arithmetic mean standard deviation	 51.5 ± 8.8	 -	
Gender categorical Units: Subjects			
Female Male	26 0	26 0	

Subject analysis sets

Subject analysis set title	Afatinib Once Daily (OD). Afatinib+V (Vinorelbine).
Subject analysis set type	Safety analysis

Subject analysis set description:

Part A: Patients received Afatinib tablets, 40 mg taken orally Once Daily (OD) until Progression of their Disease (PD). In case of treatment-related AEs, the 40 mg dose could be reduced by increments of 10 mg to 30 mg once daily or 20 mg once daily. Part B: Upon first Progression of Disease (PD), patients could enter Part B of the study, during which they continued to be treated with Afatinib and additionally were treated with Vinorelbine 25 mg/m2 per week via intravenous (i.v) infusion. Patients treated with Afatinib and Vinorelbine combination therapy could continue to receive treatment until second progression of disease, intolerable side effects, or withdrawal of consent.

Reporting group values	Afatinib Once Daily (OD). Afatinib+V (Vinorelbine).		
Number of subjects	26		
Age categorical Units: Subjects			

Age continuous			
TRT A Treated set - TS (Part A): All patients who were documented to have taken at least one dose of Afatinib in Part A. TRT B Treated set (Part B): All patients who received at least one dose each of Afatinib and Vinorelbine in Part B.			
Units: years arithmetic mean	 51.5		

standard deviation	± 8.8		

Gender categorical Units: Subjects			
Female	26		
Male	0		

End points

End points reporting groups

Reporting group title	Part A: Afatinib Once Daily (OD).

Reporting group description:

Part A: Patients received Afatinib tablets, 40 mg taken orally Once Daily (OD) until Progression of their Disease (PD). In case of treatment-related adverse events (AEs), the 40 mg dose could be reduced by increments of 10 mg to 30 mg once daily or 20 mg once daily. Patients were treated until PD in Part A, then they could continue with Afatinib and Vinorelbine in Part B.

Reporting group title	Part B: Afatinib+V (Vinorelbine).

Reporting group description:

Part B: Upon first Progression of Disease (PD), patients could enter Part B of the study, during which they continued to be treated with Afatinib at the previously applied dose in Part A and additionally were treated with Vinorelbine 25 mg/m2 per week via intravenous (i.v) infusion. Patients treated with Afatinib and Vinorelbine combination therapy could continue to receive treatment until second progression of disease, intolerable side effects, or withdrawal of consent. A patient was deemed to have completed the trial once they showed progressive disease according to RECIST (1.1) in Part B.

Subject analysis set title	Afatinib Once Daily (OD). Afatinib+V (Vinorelbine).
Subject analysis set type	Safety analysis

Subject analysis set description:

Part A: Patients received Afatinib tablets, 40 mg taken orally Once Daily (OD) until Progression of their Disease (PD). In case of treatment-related AEs, the 40 mg dose could be reduced by increments of 10 mg to 30 mg once daily or 20 mg once daily. Part B: Upon first Progression of Disease (PD), patients could enter Part B of the study, during which they continued to be treated with Afatinib and additionally were treated with Vinorelbine 25 mg/m2 per week via intravenous (i.v) infusion. Patients treated with Afatinib and Vinorelbine combination therapy could continue to receive treatment until second progression of disease, intolerable side effects, or withdrawal of consent.

Primary: Part A: Clinical Benefit (CB) Assessed by Complete Response (CR), Partial Response (PR) or Stable Disease (SD) for at least 6 Months Using the Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

End point title	Part A: Clinical Benefit (CB) Assessed by Complete Response (CR), Partial Response (PR) or Stable Disease (SD) for at least 6 Months Using the Response Evaluation Criteria in Solid Tumours (RECIST 1.1).[1]

End point description:

Tumour response was assessed separately for Part A and Part B according to the Response Evaluation Criteria in SolidTumors (RECIST) version 1.1. The primary endpoint of this study was confirmed clinical benefit, as assessed by stable disease for at least 6 months (defined as >182 days), partial response (PR), or complete response (CR) according to RECIST version 1.1 (only confirmed responses were considered). The Confidence Interval (CI) is Exact CI.

End point type	Primary

End point timeframe:

This endpoint was assessed between the from first administration of trial medication in Part A and the earliest of PD, death or start of next treatment (either Part B combination therapy or new anti-cancer therapy) up to 929 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 was tested.

End point values	Part A: Afatinib Once Daily (OD).			
Subject group type	Reporting group			
Number of subjects analysed	26[2]			
Units: Percentage of participants				
number (confidence interval 95%)	35 (17 to 56)			

Notes:

[2] - Part A: TS

Statistical analyses

No statistical analyses for this end point

Primary: Part B: Clinical Benefit (CB) Assessed by Complete Response (CR), Partial Response (PR) or Stable Disease (SD) for at least 6 Months Using the Response Evaluation Criteria in Solid Tumours (RECIST 1.1).

End point title	Part B: Clinical Benefit (CB) Assessed by Complete Response (CR), Partial Response (PR) or Stable Disease (SD) for at least 6 Months Using the Response Evaluation Criteria in Solid Tumours (RECIST 1.1).[3]

End point description:

Tumour response was assessed separately for Part A and Part B according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The primary endpoint of this study was confirmed clinical benefit, as assessed by stable disease for at least 6 months (defined as >182 days), partial response (PR), or complete response (CR) according to RECIST version 1.1 (only confirmed responses were considered). The Confidence Interval (CI) is Exact CI.

End point type	Primary

End point timeframe:

This endpoint was recorded from first administration of trial medication in Part B until the earliest of PD, death or start of new anti-cancer therapy up to 929 days.

Notes:

[3] - 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 was tested.

End point values	Part B: Afatinib+V (Vinorelbine).			
Subject group type	Reporting group			
Number of subjects analysed	10[4]			
Units: Percentage of participants				
number (confidence interval 95%)	20 (3 to 56)			

Notes:

[4] - Part B: TS

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Confirmed Objective Response (OR) Assessed by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours Version 1.1).

End point title	Part A: Confirmed Objective Response (OR) Assessed by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours Version 1.1).

End point description:

Objective response was defined on a patient level as a best response of CR or PR. The Confidence Interval (CI) is Exact CI.

End point type	Secondary

End point timeframe:

This endpoint was recorded from first administration of trial medication until the earliest of disease progression, death or start of next treatment (either Part B combination therapy or new anti-cancer therapy) up to 929 days.

End point values	Part A: Afatinib Once Daily (OD).			
Subject group type	Reporting group			
Number of subjects analysed	26[5]			
Units: Percentage of participants				
number (confidence interval 95%)	31 (14 to 52)			

Notes:

[5] - Part A: TS

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Confirmed Objective Response (OR) Assessed by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours Version 1.1).

End point title	Part B: Confirmed Objective Response (OR) Assessed by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours Version 1.1).

End point description:

Objective response was defined on a patient level as a best response of CR or PR. The Confidence Interval (CI) is Exact CI.

End point type	Secondary

End point timeframe:

This endpoint was recorded from first administration of trial medication in Part B and until the earliest of disease progression, death or start of new anti-cancer therapy up to 929 days.

End point values	Part B: Afatinib+V (Vinorelbine).			
Subject group type	Reporting group			
Number of subjects analysed	10[6]			
Units: Percentage of participants				
number (confidence interval 95%)	10 (0 to 45)			

Notes:

[6] - Part B: TS

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Unconfirmed Objective Response (OR) Assessed by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours Version 1.1).

End point title	Part A: Unconfirmed Objective Response (OR) Assessed by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours Version 1.1).

End point description:

Objective response was defined on a patient level as a best response of CR or PR. The Confidence Interval (CI) is Exact CI.

End point type	Secondary

End point timeframe:

This endpoint was recorded from first administration of trial medication until the earliest of PD, death or start of next treatment (either Part B combination therapy or new anti-cancer therapy) up to 929 days.

End point values	Part A: Afatinib Once Daily (OD).			
Subject group type	Reporting group			
Number of subjects analysed	26[7]			
Units: Percentage of participants				
number (confidence interval 95%)	42 (23 to 63)			

Notes:

[7] - Part A: TS

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Unconfirmed Objective Response (OR) Assessed by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours Version 1.1).

End point title	Part B: Unconfirmed Objective Response (OR) Assessed by RECIST 1.1 (Response Evaluation Criteria in Solid Tumours Version 1.1).

End point description:

Objective response was defined on a patient level as a best response of CR or PR. The Confidence Interval (CI) is Exact CI.

End point type	Secondary

End point timeframe:

This endpoint was recorded from first administration of trial medication in Part B and until the earliest of PD, death or start of new anti-cancer therapy up to 929 days.

End point values	Part B: Afatinib+V (Vinorelbine).			
Subject group type	Reporting group			
Number of subjects analysed	10[8]			
Units: Percentage of participants				
number (confidence interval 95%)	30 (7 to 65)			

Notes:

[8] - Part B: TS

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Duration of Unconfirmed Objective Response.

End point title	Part B: Duration of Unconfirmed Objective Response.

End point description:

Objective response was defined on a patient level as a best response of CR or PR. Duration of objective response was measured from the time of first unconfirmed objective response to the time of progression or death (or date of censoring for PFS).

End point type	Secondary

End point timeframe:

From first drug administration until end of Part B, up to 929 days.

End point values	Part B: Afatinib+V (Vinorelbine).			
Subject group type	Reporting group			
Number of subjects analysed	3[9]			
Units: Days				
median (confidence interval 95%)	57 (56 to 140)			

Notes:

[9] - Part B: TS.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Duration of Unconfirmed Objective Response.

End point title	Part A: Duration of Unconfirmed Objective Response.

End point description:

Objective response was defined on a patient level as a best response of CR (Complete Response) or PR (Partial Response). Duration of objective response was measured from the time of first unconfirmed objective response to the time of progression or death (or date of censoring for PFS-Progression Free Survival). 99999: Median is not calculable as the KM probability never falls to 0.5 therefore it can't be estimated.

End point type	Secondary

End point timeframe:

From first drug administration until end of Part A, up to 929 days.

End point values	Part A: Afatinib Once Daily (OD).			
Subject group type	Reporting group			
Number of subjects analysed	11[10]			
Units: Days				
median (confidence interval 95%)	99999 (57 to 99999)			

Notes:
[10] - Part A: TS.

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Progression Free Survival.

End point title	Part A: Progression Free Survival.

End point description:

PD was evaluated according to the RECIST version 1.1. For patients with a known date of progression (or death), PFS was the earlier of date of progression or death - date of first administration + 1. The date of progression and date of first administration referred to the respective part of the study A.

End point type	Secondary

End point timeframe:

From first drug administration until end of Part A, up to 713 days.

End point values	Part A: Afatinib Once Daily (OD).			
Subject group type	Reporting group			
Number of subjects analysed	26[11]			
Units: Days				
median (confidence interval 95%)	110.5 (58 to 386)			

Notes:
[11] - Part A: TS

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Progression Free Survival.

End point title	Part B: Progression Free Survival.

End point description:

PD was evaluated according to the RECIST version 1.1. For patients with a known date of progression (or death), PFS was the earlier of date of progression or death - date of first administration + 1. The date of progression and date of first administration referred to the respective part of the study B.

End point type	Secondary

End point timeframe:

From first drug administration until end of Part B, up to 230 days.

End point values	Part B: Afatinib+V (Vinorelbine).			
Subject group type	Reporting group			
Number of subjects analysed	10[12]			
Units: Days				
median (confidence interval 95%)	106 (36 to 190)			

Notes:

[12] - Part B: TS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival Over the Whole Sudy.

End point title	Progression Free Survival Over the Whole Sudy.

End point description:

PD was evaluated according to the RECIST version 1.1. Number of days from the start of monotherapy to the date of second PD.

End point type	Secondary

End point timeframe:

From first drug administration until end of study, up to 700 days.

End point values	Afatinib Once Daily (OD). Afatinib+V (Vinorelbine).			
Subject group type	Subject analysis set			
Number of subjects analysed	26[13]			
Units: Days				
median (confidence interval 95%)	253 (166 to 713)			

Notes:

[13] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A: From first study drug administration in Part A to last study drug administration in Part A + up to 28 days (max. 728). Part B: From first study drug administration in Part B to last study drug administration in Part B + up to 28 days (max. 265).

Adverse event reporting additional description:

The additional 28 days is the residual effect period which was added to the last study drug administration in each part. This may have been truncated in Part A where patients started Vinorelbine prior to the 28 days elapsing.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Part A: Afatinib Once Daily (OD).

Reporting group description:

Part A: Patients received Afatinib tablets, 40 mg taken orally Once Daily (OD) until progression of their disease. In case of treatment-related AEs, the 40 mg dose could be reduced by increments of 10 mg to 30 mg once daily or 20 mg once daily.

Reporting group title	Part B: Afatinib+V (Vinorelbine).

Reporting group description:

Part B: Upon first Progression of Disease (PD), patients could enter Part B of the study, during which they continued to be treated with Afatinib and additionally were treated with Vinorelbine 25 mg/m2 per week via intravenous (i.v) infusion. Patients treated with Afatinib and Vinorelbine combination therapy could continue to receive treatment until second progression of disease, intolerable side effects, or withdrawal of consent.

Serious adverse events	Part A: Afatinib Once Daily (OD).	Part B: Afatinib+V (Vinorelbine).	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 26 (46.15%)	4 / 10 (40.00%)	
number of deaths (all causes)	5	6	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Metastases to liver			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hepatic haematoma			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 26 (11.54%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 26 (11.54%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic lesion			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A: Afatinib Once Daily (OD).	Part B: Afatinib+V (Vinorelbine).	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 26 (100.00%)	10 / 10 (100.00%)	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Catheter site erythema			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	4 / 26 (15.38%)	5 / 10 (50.00%)	
occurrences (all)	5	5	
Mucosal inflammation			
subjects affected / exposed	10 / 26 (38.46%)	3 / 10 (30.00%)	
occurrences (all)	12	3	
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 26 (7.69%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 26 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	3	
Dysphonia			

subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	4 / 26 (15.38%)	0 / 10 (0.00%)	
occurrences (all)	7	0	
Pleural effusion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rhinorrhoea			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 26 (15.38%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 26 (15.38%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	7 / 26 (26.92%)	4 / 10 (40.00%)	
occurrences (all)	11	4	
White blood cell count decreased			

subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Fall			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Procedural haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 26 (7.69%)	3 / 10 (30.00%)	
occurrences (all)	3	3	
Headache			
subjects affected / exposed	3 / 26 (11.54%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Memory impairment			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	4 / 26 (15.38%)	5 / 10 (50.00%)	
occurrences (all)	4	6	
Neutropenia			
subjects affected / exposed	1 / 26 (3.85%)	8 / 10 (80.00%)	
occurrences (all)	1	29	
Eye disorders			
Dry eye			
subjects affected / exposed	3 / 26 (11.54%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Panophthalmitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 26 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	3	
Abdominal pain upper			
subjects affected / exposed	2 / 26 (7.69%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	23 / 26 (88.46%)	6 / 10 (60.00%)	
occurrences (all)	75	8	
Dry mouth			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	7 / 26 (26.92%)	5 / 10 (50.00%)	
occurrences (all)	9	8	
Stomatitis			
subjects affected / exposed	3 / 26 (11.54%)	1 / 10 (10.00%)	
occurrences (all)	3	3	
Vomiting			
subjects affected / exposed	7 / 26 (26.92%)	1 / 10 (10.00%)	
occurrences (all)	9	1	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Dry skin			
subjects affected / exposed	2 / 26 (7.69%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Dermatitis acneiform			
subjects affected / exposed	5 / 26 (19.23%)	0 / 10 (0.00%)	
occurrences (all)	5	0	
Erythema			
subjects affected / exposed	3 / 26 (11.54%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Fungating wound			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hand dermatitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 26 (11.54%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Pruritus			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Rash			
subjects affected / exposed	17 / 26 (65.38%)	1 / 10 (10.00%)	
occurrences (all)	21	2	
Skin lesion			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Myalgia			
subjects affected / exposed	1 / 26 (3.85%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Pain in extremity			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Cystitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Cellulitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Eye infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	9 / 26 (34.62%)	0 / 10 (0.00%)	
occurrences (all)	9	0	
Rhinitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 26 (7.69%)	2 / 10 (20.00%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	10 / 26 (38.46%)	2 / 10 (20.00%)	
occurrences (all)	11	2	
Hypomagnesaemia			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	5 / 26 (19.23%)	1 / 10 (10.00%)	
occurrences (all)	7	1	
Hyponatraemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2012	This amendment introduced a number of minor clarifications or updates of study procedures, administrative changes (such as updating the address of the coordinating investigator and including a citation for recently published data in place of previously unpublished data), and corrections to ensure consistency between the synopsis and the main text of the protocol and between different sections of the protocol. Changes to study procedures included the following: 1. A fresh tissue biopsy could be taken up to 2 days before C1V1. 2. No ECG was required at Day 15 of Course 1 in Part B. 3. Dispensing of trial medication was not required at the EOT visit in Part B. 4. It was clarified that patients having a short course palliative radiotherapy had to have a tumour assessment within 14 days of the first dose of Vinorelbine. 5. A statement on risk of keratitis and ulcerative keratitis was added since the European Medicines Agency (EMA) has requested a class labelling following treatment with currently approved EGFR inhibitors for cancer. 6. Exclusion criterion no. 7 was clarified: bilateral primary breast cancer, metastases to the contralateral breast. 7. Exclusion criterion no. 14 and the text of the CTP regarding dose adjustments with Vinorelbine was updated to be consistent with a newly released SmPC for Vinorelbine. 8. Exclusion criterion no. 17 was amended to allow higher values of ALT/AST (changed from 2.5 to 3 x ULN). 9. Exclusion criterion no. 26 was clarified to indicate that Trastuzumab failure patients had to have received Trastuzumab. 10. The time between first and second dose of afatinib could be less than 24 h. 11. The type of MRI to be used to assess brain lesions was updated. 12. The reporting of the worsening of underlying disease or other pre-existing conditions, and the change in vital signs, ECG, physical examination and laboratory tests results was amended as requested by regulatory authorities.
01 July 2013	This amendment introduced major changes to the study design. The reasons for the changes were slow recruitment of Trastuzumab-failure patients into Part A of the study (7 in total at 17 Jun 2013) plus a change in the benefit/risk of the combination of Afatinib and Vinorelbine (experimental arm). For BI trial 1200.75, an independent DMC conducted a benefit risk analysis when over half of the planned number of patients had been enrolled. The PFS analysis showed a low likelihood of the 1200.75 study meeting the pre-defined criteria for increased efficacy combined with an increased rate of treatment discontinuation and dose reduction and a higher rate of SAEs and deaths in the Afatinib and Vinorelbine arm of the study. The DMC recommended discontinuing recruitment into the 1200.75 trial. Boehringer Ingelheim decided to stop further randomisation into trial 1200.75 and to discontinue further treatment with the combination of Afatinib and Vinorelbine as of 26 Apr 2013. Boehringer Ingelheim decided as a precautionary measure, to stop the inclusion of new patients into Part B of the present study on 03 May 2013. Also, any patients in screening for Part B at that date were not permitted to start treatment. Due to the slow recruitment, it was also decided to stop further inclusion of patients into Part A. In addition, it was clarified that tumour assessments were to be performed in Part B every 8 weeks from the first dose of Vinorelbine. Also, precautionary information added regarding ILD (in line with the standard wording in other Afatinib trials) and keratitis (at the request of the French Health Authority for all Afatinib trials).

10 April 2014	After the introduction of protocol amendment 2 recruitment for trial 1200.89 was ceased before it was fully completed. Therefore when protocol amendment 3 was implemented, there were only a few patients still receiving trial medication. Rather than perform the primary analysis and update it shortly thereafter, it was considered better to wait until most or all patients had progressed or started further treatment. No changes were made to the analysis only to the timing. To allow flexibility as to when the primary analysis was to be performed, the sentence regarding timing was updated. Additionally, collection of Observation Period data was no longer considered necessary. Patients still benefiting from treatment were to continue to receive trial medication. However, once they ceased trial medication they were to complete their study participation at the time of their last follow-up visit and did not enter the observation period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 May 2013	Boehringer Ingelheim decided to stop further randomisation into that trial and to discontinue further treatment with the combination of afatinib and vinorelbine as of 26 Apr 2013. Boehringer Ingelheim decided as a precautionary measure, to stop the inclusion of new patients into Part B of the 1200.89 study on 03 May 2013. Also, any patients in screening for Part B at that date were not permitted to start treatment. Due to the slow recruitment, it was also decided to stop further inclusion of patients into Part A.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Boehringer Ingelheim (BI) decided to stop further inclusion of patients and stop further treatment with the combination of Afatinib and Vinorelbine as of 03-May-2013. Recruitment into the trial was stopped by amendment in Jul 2013.

Notes: