Clinical trial results:
An open-label, single-arm phase IV study to assess the efficacy and safety of afatinib as second-line therapy for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring an Epidermal growth factor receptor (EGFR) mutation (Del19 or L858R) who have failed first-line treatment with platinum-based chemotherapy

Summary

EudraCT number	2014-001077-14
Trial protocol	RO PL
Global end of trial date	13 June 2017

Results information

Result version number	v1
This version publication date	21 June 2018
First version publication date	21 June 2018

Trial information

Trial identification

Sponsor protocol code	1200.217

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02208843
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	03 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 May 2017
Global end of trial reached?	Yes
Global end of trial date	13 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this single-arm, open-label trial was to assess the efficacy and safety of afatinib as second-line treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harbouring an epidermal growth factor receptor (EGFR) mutation (Del19 and/or L858R) who had failed first-line platinumbased chemotherapy.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 November 2014
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	Egypt: 17
Country: Number of subjects enrolled	Philippines: 6
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Romania: 15
Country: Number of subjects enrolled	Serbia: 6
Country: Number of subjects enrolled	Thailand: 19
Worldwide total number of subjects	70
EEA total number of subjects	22

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)	46
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

An open-label, single-arm phase IV, a total of 70 patients were enrolled by multinational trial at 24 sites in 7 countries. Of the 70 enrolled patients, 60 patients were entered the trial and 60 were treated.

Pre-assignment

Screening details:

All patients were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that all subjects met all inclusion/exclusion criteria. Subjects were not to be entered to trial treatment if any one of the specific entry criteria were not met.

Period 1

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

Blinding implementation details:

This is Non-Randomised and Non controlled trial

Arms

Arm title	Afatinib 40 mg

Arm description:

All patients received continuous daily treatment with Afatinib at a starting dose of 40 miligram (mg), treatment interruption and reduction scheme to 30 mg and then to 20 mg were permitted to manage treatment-related adverse events (AEs). Patients were orally administered with the film coated tablet once a day without food.

Arm type	Active comparator
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:

All patients were orally received continuous daily treatment with Afatinib at a starting dose of 40 miligram (mg), treatment interruption and reduction scheme to 30 mg and then to 20 mg were permitted to manage treatment-related adverse events (AEs).

Number of subjects in period 1[1]	Afatinib 40 mg
Started	60
Completed	0
Not completed	60
Adverse event, serious fatal	6
Consent withdrawn by subject	1
Adverse event, non-fatal	6
Progression disease according to RECIST	24
Switched to commercial afatinib	20

Clinical symptoms of progression	2
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 patients who were randomized after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib 40 mg

Reporting group description:

All patients received continuous daily treatment with Afatinib at a starting dose of 40 miligram (mg), treatment interruption and reduction scheme to 30 mg and then to 20 mg were permitted to manage treatment-related adverse events (AEs). Patients were orally administered with the film coated tablet once a day without food.

Reporting group values	Afatinib 40 mg	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
Age Continuous			
Treated Set (TS): The TS includes all patients who were documented to have taken at least 1 dose of afatinib.			
Units: years arithmetic mean standard deviation	 59.9 ± 9.8	 -	
Sex: Female, Male			
Number of subjects is categorized as Male or Female.			
Units: Subjects			
Female	33	33	
Male	27	27	
Race (NIH/OMB)			
Number of subjects is categorized for race data. Ethnicity data were not collected for this study.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	19	19	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	41	41	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Afatinib 40 mg

Reporting group description:

All patients received continuous daily treatment with Afatinib at a starting dose of 40 miligram (mg), treatment interruption and reduction scheme to 30 mg and then to 20 mg were permitted to manage treatment-related adverse events (AEs). Patients were orally administered with the film coated tablet once a day without food.

Primary: Objective tumour response (complete response [CR], partial response [PR]) as assessed by the investigator according to the RECIST version 1.1

End point title	Objective tumour response (complete response [CR], partial response [PR]) as assessed by the investigator according to the RECIST version 1.1[1]

End point description:

As Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by Magnetic resonance imaging (MRI): Complete Response (CR), disappearance of all target lesions; Partial Response (PR), =30% decrease in the sum of the longest diameter of target lesions

End point type	Primary

End point timeframe:

Post baseline tumour-imaging was performed at every 8 weeks until Week 56 and then every 12 weeks; up to 802 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 were tested.

End point values	Afatinib 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	60[2]			
Units: Percentage of participants				
number (confidence interval 95%)	50 (36.8 to 63.2)			

Notes:

[2] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) as assessed by the investigator according to RECIST 1.1.

End point title	Progression-free survival (PFS) as assessed by the investigator according to RECIST 1.1.

End point description:

Progression-free survival (PFS) is the time from treatment start to disease progression (or death if the patient died before progression). PFS as assessed based on investigator review according to the response evaluation criteria in solid tumours (RECIST) version 1.1.

End point type	Secondary

End point timeframe:

Post baseline tumour-imaging was performed at every 8 weeks until Week 56 and then every 12 weeks;

End point values	Afatinib 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	60[3]			
Units: Months				
median (confidence interval 95%)	10.94 (6.44 to 13.20)			

Notes:

[3] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control (CR, PR, stable disease [SD]) as assessed by the investigator according to RECIST 1.1

End point title	Disease control (CR, PR, stable disease [SD]) as assessed by the investigator according to RECIST 1.1

End point description:

As Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.0) for target lesions and assessed by MRI: Complete Response (CR), disappearance of all target lesions; Partial Response (PR), =30% decrease in the sum of the longest diameter of target 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:

Post baseline tumour-imaging was performed at every 8 weeks until Week 56 and then every 12 weeks; up to 802 days

End point values	Afatinib 40 mg			
Subject group type	Reporting group			
Number of subjects analysed	60[4]			
Units: Percentage of participants				
number (confidence interval 95%)	83.3 (71.5 to 91.7)			

Notes:

[4] - TS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 28 days after last drug administration, up to 830 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Afatinib 40 mg

Reporting group description:

All patients received continuous daily treatment with Afatinib at a starting dose of 40 miligram (mg), treatment interruption and reduction scheme to 30 mg and then to 20 mg were permitted to manage treatment-related adverse events (AEs). Patients were orally administered with the film coated tablet once a day without food.

Serious adverse events	Afatinib 40 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 60 (35.00%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 3		
Malignant pleural effusion			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Fatigue			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Myocardial infarction			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Brain oedema			

subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cerebrovascular accident			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Epilepsy			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorder			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurological decompensation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Seizure			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Acute hepatic failure			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Electrolyte imbalance			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Afatinib 40 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 60 (91.67%)		
Investigations			

Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	8		
Weight decreased			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 60 (20.00%)		
occurrences (all)	13		
Leukopenia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	15		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	11 / 60 (18.33%)		
occurrences (all)	15		
Mucosal inflammation			
subjects affected / exposed	12 / 60 (20.00%)		
occurrences (all)	18		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	43 / 60 (71.67%)		
occurrences (all)	188		
Nausea			
subjects affected / exposed	12 / 60 (20.00%)		
occurrences (all)	14		
Stomatitis			

subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	5 / 60 (8.33%) 5 6 / 60 (10.00%) 6		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 4 / 60 (6.67%) 4		
Skin and subcutaneous tissue disorders Acne subjects affected / exposed occurrences (all) Dermatitis subjects affected / exposed occurrences (all) Dermatitis acneiform subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Nail pitting subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 4 / 60 (6.67%) 5 6 / 60 (10.00%) 8 9 / 60 (15.00%) 13 5 / 60 (8.33%) 5 4 / 60 (6.67%) 4 5 / 60 (8.33%) 6 18 / 60 (30.00%) 26		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 4 / 60 (6.67%) 4		
Infections and infestations			

Paronychia			
subjects affected / exposed	14 / 60 (23.33%)		
occurrences (all)	15		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Hyperglycaemia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Hypocalcaemia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	14 / 60 (23.33%)		
occurrences (all)	22		
Hypomagnesaemia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Hyponatraemia			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported