Clinical trial results:
An open label trial of afatinib (Giotrif®) in treatment-naïve (1st line) or chemotherapy pre-treated patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s)

Summary

EudraCT number	2009-017661-34
Trial protocol	CZ HU IT ES AT GR PT PL
Global end of trial date	06 March 2024

Results information

Result version number	v1
This version publication date	16 March 2025
First version publication date	16 March 2025

Trial information

Trial identification

Sponsor protocol code	1200.55

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01853826
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	Boehringer Ingelheim, Boehringer Ingelheim, Call Center, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, 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 May 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2018
Global end of trial reached?	Yes
Global end of trial date	06 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety, tolerability and efficacy of afatinib (Giotrif®) in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutation(s) and have never been treated with an EGFR-tyrosine kinase inhibitors.

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. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumor associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 August 2013
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: 15
Country: Number of subjects enrolled	Austria: 26
Country: Number of subjects enrolled	Czechia: 22
Country: Number of subjects enrolled	Greece: 13
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Israel: 25
Country: Number of subjects enrolled	Italy: 168
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Portugal: 12
Country: Number of subjects enrolled	Russian Federation: 85
Country: Number of subjects enrolled	Spain: 85
Worldwide total number of subjects	495
EEA total number of subjects	370

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)	245
From 65 to 84 years	245
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Open-label, multicentre, single-arm trial to evaluate the safety, tolerability and efficacy of afatinib in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutation(s) who had never been treated with an EGFR tyrosine kinase inhibitor (TKI).

Pre-assignment

Screening details:

All participants were screened for eligibility prior to participation in the trial. Participants attended a specialist site which ensured that they (the participants) strictly met all inclusion and none of the exclusion criteria. Participants were not to be allocated to a treatment group if any of the entry criteria were violated.

Period 1

Period 1 title	Entered Patients
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This study was conducted open label.

Arms

Arm title	Afatinib treated-patients

Arm description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Afatinib treated-patients
Started	481
Completed	479
Not completed	2
Not signed privacy consent form	2

Period 2

Period 2 title	Treated patients
Is this the baseline period?	Yes[1]
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This study was conducted open-label.

Arms

Arm title	Afatinib treated-patients

Arm description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

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

Dosage and administration details:

Patients received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The baseline period is on the treated set represented by the treated patient's period.

Number of subjects in period 2[2]	Afatinib treated-patients
Started	479
Completed	0
Not completed	479
Other adverse events (AE)	62
Patients who switched to commercial drug	11
Worsening or AE of underlying cancer disease	24
Patient refused to continue medication	21
Non-compliant with protocol	4
Lost to follow-up	2
Progressive disease	342
Other than listed	13

Notes:

[2] - 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: From the 495 patients screened, 479 started the trial treatment.

Baseline characteristics

Reporting groups

Reporting group title	Afatinib treated-patients

Reporting group description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Reporting group values	Afatinib treated-patients	Total	
Number of subjects	479	479	
Age categorical			
Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	238	238	
From 65-84 years	236	236	
85 years and over	5	5	
Age Continuous			
Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.			
Units: years			
arithmetic mean	64.2		
standard deviation	± 10.9	-	
Sex: Female, Male			
Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.			
Units: Subjects			
Female	314	314	
Male	165	165	
Race (NIH/OMB)			
Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	10	10	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	3	3	
White	465	465	

More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Afatinib treated-patients

Reporting group description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Reporting group title	Afatinib treated-patients

Reporting group description:

Patients diagnosed with EGFR mutation positive non-small cell lung cancer (NSCLC) locally advanced or metastatic who have never been treated with EGFR tyrosine kinase inhibitors (TKI) received a daily dose of 40 milligrams (mg) of afatinib (Giotrif®), in the form of film-coated tablet over a 28 day cycle. Afatinib was taken orally with 250 milliliters (mL) of water at the same time of the day and without eating anything for at least 3 hours. Patients continued on treatment for as long as there was no disease progression or no other trial withdrawal criteria. The dose was reduced to 30 mg or 20 mg once daily when the initial dose was not tolerated by the patient.

Primary: Number of patients with adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0

End point title	Number of patients with adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0[1]

End point description:

Number of patients with any treatment emergent adverse event (AE) according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

The analysis was performed on the treated set. The treated set is defined by all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.

End point type	Primary

End point timeframe:

From first drug administration to last drug administration plus 28 days of residual effect period. Up to 3866 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 analyzed only descriptively.

End point values	Afatinib treated-patients			
Subject group type	Reporting group			
Number of subjects analysed	479			
Units: Participants	478			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 28 days after the last drug administration.

Adverse event reporting additional description:

Treated set (TS): all patients who were dispensed afatinib and are documented to have taken at least one dose of afatinib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Afatinib 40 mg

Reporting group description: -

Serious adverse events	Afatinib 40 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	210 / 479 (43.84%)		
number of deaths (all causes)	127		
number of deaths resulting from adverse events	71		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer pain			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chromophobe renal cell carcinoma			

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endometrial sarcoma				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung adenocarcinoma				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant melanoma				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningioma				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningioma benign				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to central nervous system				
subjects affected / exposed	11 / 479 (2.30%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 1			
Metastases to liver				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastases to meninges				

subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Metastases to pancreas				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metastasis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ovarian granulosa cell tumour				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Transitional cell carcinoma				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Malignant neoplasm progression				
subjects affected / exposed	36 / 479 (7.52%)			
occurrences causally related to treatment / all	0 / 36			
deaths causally related to treatment / all	0 / 29			
Vascular disorders				
Venous thrombosis				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Deep vein thrombosis				

subjects affected / exposed	4 / 479 (0.84%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral vascular disorder			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena cava syndrome			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vena cava thrombosis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgery			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Death				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Disease progression				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Fatigue				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Condition aggravated				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Chest pain				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Asthenia				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	11 / 479 (2.30%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 4			
Hyperpyrexia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple organ dysfunction syndrome				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	4 / 479 (0.84%)			
occurrences causally related to treatment / all	2 / 4			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Cervical dysplasia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystocele				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uterine prolapse				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Acute respiratory failure				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 2			
Atelectasis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	11 / 479 (2.30%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Interstitial lung disease				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	16 / 479 (3.34%)			
occurrences causally related to treatment / all	0 / 17			
deaths causally related to treatment / all	0 / 0			
Pleurisy				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				

subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 1			
Pneumothorax				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	13 / 479 (2.71%)			
occurrences causally related to treatment / all	0 / 13			
deaths causally related to treatment / all	0 / 3			
Pulmonary thrombosis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	6 / 479 (1.25%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 6			
Hydrothorax				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Behaviour disorder				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bradyphrenia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Confusional state				

subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Hallucination				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device dislocation				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood creatine phosphokinase increased				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			

C-reactive protein increased				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Weight decreased				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Radius fracture				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Patella fracture				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Limb injury				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Femur fracture				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Fall				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Craniofacial fracture				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Concussion				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Accidental poisoning				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Toxicity to various agents				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thoracic vertebral fracture				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral nerve injury				

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute coronary syndrome				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ventricular hypokinesia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pericardial effusion				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Left ventricular dilatation				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiopulmonary failure				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Atrial fibrillation				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac tamponade				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Hemiparesis				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Aphasia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral haemorrhage				

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	5 / 479 (1.04%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 4			
Cerebrovascular disorder				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cognitive disorder				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 1			
Dementia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Embolic stroke				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Epilepsy				

subjects affected / exposed	4 / 479 (0.84%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 1			
Generalised tonic-clonic seizure				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	4 / 479 (0.84%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Neuropathy peripheral				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal cord compression				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Memory impairment				

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myelopathy				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Neurological decompensation				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Somnolence				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Thrombocytopenia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Coagulopathy				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disseminated intravascular coagulation				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Glaucoma				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	16 / 479 (3.34%)		
occurrences causally related to treatment / all	17 / 18		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	7 / 479 (1.46%)		
occurrences causally related to treatment / all	6 / 9		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Retroperitoneal haematoma			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rectal haemorrhage			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophageal obstruction			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Odynophagia			

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal infarction				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Gastritis erosive				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric perforation				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 479 (0.21%)		
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 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 479 (0.21%)		
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	4 / 479 (0.84%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	0 / 0		

Hydronephrosis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	8 / 479 (1.67%)		
occurrences causally related to treatment / all	3 / 8		
deaths causally related to treatment / all	0 / 1		
Urinary retention			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 479 (0.63%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pathological fracture			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	9 / 479 (1.88%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 3		

Pneumocystis jirovecii infection			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Paronychia			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oral herpes			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Mastoiditis			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 479 (0.42%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Enterocolitis bacterial			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear infection bacterial			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Conjunctivitis			

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridial infection				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	2 / 479 (0.42%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cavernous sinus thrombosis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bacteraemia				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abscess neck				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abscess				

subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	5 / 479 (1.04%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Sepsis				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	3 / 479 (0.63%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia cytomegaloviral				
subjects affected / exposed	1 / 479 (0.21%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Metabolism and nutrition disorders				
Decreased appetite				

subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	6 / 479 (1.25%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Electrolyte imbalance			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	1 / 479 (0.21%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Iron deficiency			
subjects affected / exposed	1 / 479 (0.21%)		
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	268 / 479 (55.95%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	35 / 479 (7.31%)		
occurrences (all)	101		
Mucosal inflammation			
subjects affected / exposed	54 / 479 (11.27%)		
occurrences (all)	145		
Pyrexia			
subjects affected / exposed	30 / 479 (6.26%)		
occurrences (all)	76		
Asthenia			
subjects affected / exposed	52 / 479 (10.86%)		
occurrences (all)	173		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	238 / 479 (49.69%)		
occurrences (all)	3275		
Nausea			
subjects affected / exposed	32 / 479 (6.68%)		
occurrences (all)	111		
Stomatitis			
subjects affected / exposed	42 / 479 (8.77%)		
occurrences (all)	126		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	36 / 479 (7.52%)		
occurrences (all)	112		
Dyspnoea			
subjects affected / exposed	30 / 479 (6.26%)		
occurrences (all)	98		
Skin and subcutaneous tissue disorders			
Skin fissures			

subjects affected / exposed	27 / 479 (5.64%)		
occurrences (all)	78		
Dermatitis acneiform			
subjects affected / exposed	28 / 479 (5.85%)		
occurrences (all)	69		
Dry skin			
subjects affected / exposed	49 / 479 (10.23%)		
occurrences (all)	111		
Pruritus			
subjects affected / exposed	29 / 479 (6.05%)		
occurrences (all)	74		
Rash			
subjects affected / exposed	143 / 479 (29.85%)		
occurrences (all)	501		
Rash papular			
subjects affected / exposed	27 / 479 (5.64%)		
occurrences (all)	52		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	41 / 479 (8.56%)		
occurrences (all)	100		
Paronychia			
subjects affected / exposed	85 / 479 (17.75%)		
occurrences (all)	236		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	27 / 479 (5.64%)		
occurrences (all)	103		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2013	Global amendment 1: Clarifications, corrections, and administrative changes, or updates to background information were made. In addition the following was implemented: - cardiac assessments (electrocardiogram (ECG) and left ventricular ejection fraction (LVEF)) were to be performed only if clinically indicated. Left ventricular dysfunction has been associated with HER2 inhibition. Based on the available clinical trial data, there as no suggestion that afatinib caused an adverse effect on cardiac contractility. However, afatinib had not been studied in patients with abnormal LVEF or those with significant cardiac history. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during afatinib treatment, should be considered. In patients that developed relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.; - reporting of serious adverse events (SAEs) after the follow-up period was clarified. The investigator did not need to actively monitor patients for AEs once the clinical trial had ended. However, if the investigator became aware of an SAE that occurred after the patient had completed the clinical trial (including any protocol required residual effect period (REP) and / or follow-up), it was to be reported by the investigator to the sponsor if considered relevant by the investigator;
05 November 2013	Global amendment 1 (continued) - new safety information was added: patients who presented with symptoms of keratitis, such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye were to be referred promptly to an ophthalmic specialist. If a diagnosis of ulcerative keratitis was confirmed, treatment with afatinib was to be interrupted or discontinued. If keratitis was diagnosed, the benefits and risks of continuing treatment with afatinib were to be carefully considered. Afatinib should be used with caution in patients with a history of keratitis, ulcerative keratitis, or severe dry eye. Contact lens use is a risk factor for keratitis and ulceration; - acceptable methods of birth control were to be used for 28 days after the end of active treatment (rather than 14 days as originally specified).
17 August 2017	Global amendment 2: In addition to clarifications, corrections, and administrative changes, or updates to background information, the following main changes, were implemented: the duration of treatment was updated to ensure an on-going supply to patients who have not yet met the criteria for ceasing study treatment and to allow completion of the trial; a planned interim analysis was added.
08 February 2021	Global amendment 3: In addition to clarifications, corrections, and administrative changes, or updates to background information, the following main changes, were implemented: shipment of medication to patients' homes (or dispensing enough medication for 2 cycles) was permitted to allow flexibility in visit conduct in case required due to pandemic or other exceptional situations to ensure patients safety by ensuring continuous treatment; the risk assessment was updated in line with updates to the Investigator Brochure, to note that gastrointestinal perforation, including fatalities, had been reported during treatment with afatinib in 0.2% of patients across all randomised controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. Patients who develop gastrointestinal perforation while taking afatinib, should permanently discontinue treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported