Clinical trial results:
LUX-Lung 7: A randomised, open-label Phase IIb trial of afatinib versus gefitinib as first-line treatment of patients with EGFR mutation positive advanced adenocarcinoma of the lung

Summary

EudraCT number	2011-001814-33
Trial protocol	SE ES DE NO GB IE
Global end of trial date	12 April 2019

Results information

Result version number	v1
This version publication date	11 April 2020
First version publication date	11 April 2020

Trial information

Trial identification

Sponsor protocol code	1200.123

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01466660
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 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, 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	08 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a randomised, open-label, phase IIb trial of afatinib to compare to gefitinib in first-line treatment setting with patients who are having epidermal growth factor receptor mutation positive advanced adenocarcinoma of the lung.

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 subjects as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 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: 33
Country: Number of subjects enrolled	Canada: 92
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Spain: 93
Country: Number of subjects enrolled	France: 56
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	China: 63
Country: Number of subjects enrolled	Taiwan: 26
Country: Number of subjects enrolled	Korea, Republic of: 89
Country: Number of subjects enrolled	Sweden: 40
Country: Number of subjects enrolled	Singapore: 31
Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	571
EEA total number of subjects	231

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)	314
From 65 to 84 years	251
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Two-arm, randomised (1:1 ratio), open-label, parallel group trial.

In the study disease response was assessed by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

This open-label trial was treated as blinded by the trial team until database lock. Blinding of trial medication was not feasible because of differences in dose adjustments (dose adjustment scheme for afatinib, gefitinib was only available in one dose strength) and limitations in gefitinib packaging.

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib

Arm description:

Afatinib film-coated tablets administered orally, once daily. Starting dose was 40 milligram (mg), dose escalation to 50mg was allowed after completing one 28-day treatment course, dose reduction to 40mg, 30mg or 20mg was required in the presence of protocol-defined adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal.

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:

Afatinib film-coated tablets administered orally, once daily. Starting dose was 40 milligram (mg), dose escalation to 50mg was allowed after completing one 28-day treatment course, dose reduction to 40mg, 30mg or 20mg was required in the presence of protocol-defined adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal.

Arm title	Gefitinib

Arm description:

Gefitinib film-coated tablets, administered orally, once daily. Starting dose was 250mg, the investigator was allowed to modify dosing in the presence of drug-related adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal.

Arm type	Active comparator

Investigational medicinal product name	Gefitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Gefitinib film-coated tablets, administered orally, once daily. Starting dose was 250mg, the investigator was allowed to modify dosing in the presence of drug-related adverse events. Continuous daily dosing until disease progression, occurrence
of unacceptable adverse events, or other reason necessitating
withdrawal.

Number of subjects in period 1[1]	Afatinib	Gefitinib
Started	160	159
Completed	0	0
Not completed	160	159
Other reason not defined above	10	8
Refused continuation of trial medication	4	3
Progressive Disease (RECIST 1.1)	120	127
Other adverse event	19	18
Worsening of underlying cancer disease	5	2
Protocol deviation	2	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: 571 subjects were enrolled worldwide and thereof 252 not randomised. The remaining 319 subjects were randomised and treated.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Randomised subjects.	

Reporting group values	Overall Study	Total	
Number of subjects	319	319	
Age categorical			
Analysis set: All randomised subjects.			
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)	177	177	
From 65-84 years	138	138	
85 years and over	4	4	
Age Continuous			
Units: Years			
arithmetic mean	62.4		
standard deviation	± 11.0	-	
Sex: Female, Male			
Units:			
Female	197	197	
Male	122	122	
Race (NIH/OMB)			
Analysis set: All randomised subjects. "Unknown or Not Reported" reflects the subjects in France where race was not recorded.			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	182	182	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	102	102	
More than one race	0	0	
Unknown or Not Reported	34	34	

End points

End points reporting groups

Reporting group title	Afatinib

Reporting group description:

Afatinib film-coated tablets administered orally, once daily. Starting dose was 40 milligram (mg), dose escalation to 50mg was allowed after completing one 28-day treatment course, dose reduction to 40mg, 30mg or 20mg was required in the presence of protocol-defined adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal.

Reporting group title	Gefitinib

Reporting group description:

Gefitinib film-coated tablets, administered orally, once daily. Starting dose was 250mg, the investigator was allowed to modify dosing in the presence of drug-related adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal.

Primary: Progression-free survival

End point title	Progression-free survival

End point description:

Progression-free survival (PFS) defined as the time from date of randomisation to date of disease progression, or date of death if a patient died earlier. Participants with no event (Disease progression (PD) or death) were censored. PD was primarily evaluated for the primary analysis by an independent central imaging review according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Per RECIST version 1.1. for target lesions and assessed by Computed Tomography (CT)-scan or Magnetic Resonance Imaging (MRI): PD, At least a 20% increase in the sum of the longest diameter (SoD) of target lesions taking as reference the smallest SoD of target lesions recorded since the treatment started, together with an absolute increase in the SoD of target lesions of at least 5 millimetre (mm) or the appearance of one or more new lesions. For the final analysis (analysis cut-off date 12 April 2019) status and date of PD were determined by investigator assessment.

End point type	Primary

End point timeframe:

From first drug administration until 28 days after last drug administration + Follow-Up period for collecting information on disease progression or death, up to 2465 days.

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[1]	159[2]		
Units: Months				
median (confidence interval 95%)	12.78 (10.91 to 14.72)	11.17 (9.49 to 12.81)		

Notes:

[1] - Randomised set included all subjects randomised to receive treatment.

[2] - Randomised set included all subjects randomised to receive treatment.

Statistical analyses

Statistical analysis title	Time-to-event analysis

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

Comparison groups	Afatinib v Gefitinib

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.0891 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.822
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.655
upper limit	1.032

Notes:

[3] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Primary: Time to Treatment Failure (TTF) (main overall survival analysis cut-off date, 08 April 2016)

End point title	Time to Treatment Failure (TTF) (main overall survival analysis cut-off date, 08 April 2016)

End point description:

Time to Treatment Failure (TTF) which was the time from the date of randomisation to the date of i.e. permanent treatment discontinuation for any reason.

End point type	Primary

End point timeframe:

From first drug administration until last drug administration, up to 1482 days

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[4]	159[5]		
Units: Months				
median (confidence interval 95%)	13.67 (11.89 to 14.95)	11.53 (10.09 to 13.11)		

Notes:

[4] - Randomised set included all subjects randomised to receive treatment.

[5] - Randomised set included all subjects randomised to receive treatment.

Statistical analyses

Statistical analysis title	Time-to-event analysis

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

Comparison groups	Afatinib v Gefitinib
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0136 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.595
upper limit	0.944

Notes:

[6] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Primary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) which was defined as the time from the date of randomisation to the date of death. Participants for whom there is no evidence of death at the time of the analysis will be censored at the date that they were last known to be alive.

End point type	Primary

End point timeframe:

From first drug administration until 28 days after last drug administration + Follow-Up period for collecting information on death, up to 2465 days.

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[7]	159[8]		
Units: Months				
median (confidence interval 95%)	27.86 (25.13 to 32.85)	24.54 (20.57 to 28.88)		

Notes:

[7] - Randomised set included all subjects randomised to receive treatment.

[8] - Randomised set included all subjects randomised to receive treatment.

Statistical analyses

Statistical analysis title	Time-to-event analysis

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

Comparison groups	Afatinib v Gefitinib
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.2343 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.862
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.674
upper limit	1.101

Notes:

[9] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Secondary: Objective response rate

End point title	Objective response rate

End point description:

Objective response rate (ORR) which was defined as the number of participants with best overall response of complete response (CR) or partial response (PR) as assessed by central independent review according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. divided by the total number of participants who received treatment. Per RECIST version 1.1. for target lesions and assessed by Computed Tomography (CT)-scan or 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 from baseline. For the final analysis (analysis cut-off date 12 April 2019) objective response was determined by investigator assessment.

End point type	Secondary

End point timeframe:

From first drug administration until 28 days after last drug administration + Follow-Up period for collecting information on disease progression, further anti-cancer treatment and death, up to 2465 days.

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[10]	159[11]		
Units: Percentage of participants				
number (confidence interval 95%)	79.4 (72.3 to 85.4)	74.8 (67.4 to 81.4)		

Notes:

[10] - Randomised set included all subjects randomised to receive treatment.

[11] - Randomised set included all subjects randomised to receive treatment.

Statistical analyses

Statistical analysis title	Logistic regression analysis

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

Comparison groups	Afatinib v Gefitinib
Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.3235 [12]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.307
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.768
upper limit	2.223

Notes:

[12] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Secondary: Time to objective response

End point title	Time to objective response

End point description:

Number of participants with objective response (best overall response of complete response or partial response) to study treatment over time, cumulative number of participants is displayed. Time to objective response was defined as the time from randomisation to the first recorded objective response. For the final analysis (analysis cut-off date 12 April 2019) objective response was determined by investigator assessment.

End point type	Secondary

End point timeframe:

From first drug administration until 28 days after last drug administration + Follow-Up period for collecting information on disease progression, further anti-cancer treatment and death, up to 2465 days.

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[13]	119[14]		
Units: Participants				
Week 4	81	74		
Week 8	112	107		
Week 16	119	117		
Week 24	122	118		
Week 32	125	118		
Week 40	126	118		
Week 48	127	119		

Notes:

[13] - All randomised subjects with objective response.

[14] - All randomised subjects with objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response

End point title	Duration of objective response

End point description:

Duration of objective response defined as the time of first objective response (best overall response of complete response or partial response) to the time of progression or death, whichever occurred first (or date of censoring for progression free survival). For the final analysis (analysis cut-off date 12 April 2019) objective response was determined by investigator assessment.

End point type	Secondary

End point timeframe:

From first drug administration until 28 days after last drug administration + Follow-Up period for collecting information on disease progression, further anti-cancer treatment and death, up to 2465 days.

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127[15]	119[16]		
Units: Months				
median (confidence interval 95%)	11.86 (10.12 to 15.54)	11.07 (9.69 to 12.91)		

Notes:

[15] - All randomised subjects with objective response.

[16] - All randomised subjects with objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control

End point title	Disease control

End point description:

Percentage of participants with disease control defined as the number of participants with best overall response of complete response (CR) or partial response (PR) or stable disease (SD) as assessed by central independent review according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. divided by the total number of participants who received treatment. Per RECIST version 1.1. for target lesions and assessed by Computed Tomography (CT)-scan or 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 from baseline; Stable Disease (SD), Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Responses of SD were only considered if they occur ≥42 days from date of randomisation. For the final analysis (analysis cut-off date 12 April 2019) disease control was determined by investigator assessment.

End point type	Secondary

End point timeframe:

From first drug administration until 28 days after last drug administration + Follow-Up period for collecting information on disease progression or death, up to 2465 days.

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[17]	159[18]		
Units: Percentage of participants				
number (confidence interval 95%)	94.4 (89.6 to 97.4)	93.7 (88.7 to 96.9)		

Notes:

[17] - Randomised set included all subjects randomised to receive treatment.

[18] - Randomised set included all subjects randomised to receive treatment.

Statistical analyses

Statistical analysis title	Logistic regression analysis

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

Comparison groups	Afatinib v Gefitinib

Number of subjects included in analysis	319
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.7856 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.138
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.447
upper limit	2.896

Notes:

[19] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Secondary: Duration of disease control

End point title	Duration of disease control

End point description:

Duration of disease control defined as the time from randomisation to the time of progression or death, whichever occurred first (or date of censoring for progression free survival). For the final analysis (analysis cut-off date 12 April 2019) the status and date of disease progression were determined by investigator assessment.

All randomised subjects with disease control are all randomised subjects with best overall response of complete response or partial response or stable disease.

End point type	Secondary

End point timeframe:

From first drug administration until 28 days after last drug administration + Follow-Up period for collecting information on disease progression or death, up to 2465 days.

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[20]	149[21]		
Units: Months				
median (confidence interval 95%)	12.88 (11.14 to 14.88)	11.73 (10.58 to 14.55)		

Notes:

[20] - All randomised subjects with disease control.

[21] - All randomised subjects with disease control.

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour shrinkage (main overall survival analysis cut-off date, 08 April 2016)

End point title	Tumour shrinkage (main overall survival analysis cut-off date, 08 April 2016)

End point description:

Tumour shrinkage assessed by minimum sum of post-baseline target lesion diameters recorded after randomisation. A positive value shows a decrease in tumour size.

End point type	Secondary

End point timeframe:

From first drug administration until last drug administration, up to 1482 days

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149[22]	151[23]		
Units: millimetre (mm)				
least squares mean (confidence interval 95%)	34.79 (32.18 to 37.40)	38.25 (35.65 to 40.84)		

Notes:

[22] - All randomised subjects with tumour assessments.

[23] - All randomised subjects with tumour assessments.

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

Comparison groups	Afatinib v Gefitinib
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.0657 [24]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-3.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.13
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	1.87

Notes:

[24] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Secondary: Health-related quality of life (primary analysis cut-off date, 21 August 2015)

End point title	Health-related quality of life (primary analysis cut-off date, 21 August 2015)

End point description:

Health-related quality of life (HRQoL) measured using European Quality of life - 5 Dimensions (EQ-5D) score for United Kingdom (UK) and Belgium and European European Quality Visual Analogue Scale (EQ-VAS).

EQ-5D utility scores range from 0 (worst health) to 1 (full health).

EQ-VAS scores range from 0 (worst imaginable health state) to 100 (best imaginable health state).

Results display the mean score up to 56 weeks.

End point type	Secondary
End point timeframe:	
Every 8 weeks, up to 56 weeks	

End point values	Afatinib	Gefitinib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	160[25]	158[26]		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
EQ-5D UK utility score	0.77 (0.75 to 0.80)	0.80 (0.77 to 0.82)		
EQ-5D Belgium utility score	0.74 (0.72 to 0.77)	0.77 (0.75 to 0.80)		
EQ-VAS utility score	74.5 (72.3 to 76.6)	76.0 (73.9 to 78.1)		

Notes:

[25] - All randomised subjects with health-related quality of life data.

[26] - All randomised subjects with health-related quality of life data.

Statistical analyses

Statistical analysis title	Mixed models analysis for EQ-5D UK
Statistical analysis description:	
EQ-5D UK utility score. Exploratory trial, no formal hypotheses were tested.	
Comparison groups	Afatinib v Gefitinib
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.1422 [27]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.017

Notes:

[27] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Statistical analysis title	Mixed models analysis for EQ-5D Belgium
Statistical analysis description:	
EQ-5D Belgium utility score. Exploratory trial, no formal hypotheses were tested.	
Comparison groups	Afatinib v Gefitinib

Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.054 [28]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0
Variability estimate	Standard error of the mean
Dispersion value	0.016

Notes:

[28] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Statistical analysis title	Mixed models analysis for EQ-VAS

Statistical analysis description:

EQ-VAS utility score. Exploratory trial, no formal hypotheses were tested.

Comparison groups	Afatinib v Gefitinib
Number of subjects included in analysis	318
Analysis specification	Pre-specified
Analysis type	
P-value	≤ 0.2032 [29]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	0.8
Variability estimate	Standard error of the mean
Dispersion value	1.21

Notes:

[29] - p-value was not adjusted for multiple comparisons and was interpreted in an exploratory fashion.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration (admin) until 28 days after last drug admin, up to 2405 days.
For All-Cause Mortality: From first drug admin until 28 days after last drug admin + Follow-Up period for collecting information on death, up to 2465 days.

Adverse event reporting additional description:

Treated set included all subjects who were dispensed with and documented to have taken at least one dose of study medication. This set of subjects was used for the evaluation of safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Afatinib

Reporting group description:

Afatinib film-coated tablets administered orally, once daily. Starting dose was 40 milligram (mg), dose escalation to 50mg was allowed after completing one 28-day treatment course, dose reduction to 40mg, 30mg or 20mg was required in the presence of protocol-defined adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal.

Reporting group title	Gefitinib

Reporting group description:

Gefitinib film-coated tablets, administered orally, once daily. Starting dose was 250mg, the investigator was allowed to modify dosing in the presence of drug-related adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal.

Serious adverse events	Afatinib	Gefitinib	
Total subjects affected by serious adverse events			
subjects affected / exposed	75 / 160 (46.88%)	64 / 159 (40.25%)	
number of deaths (all causes)	126	132	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	7 / 160 (4.38%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 5	0 / 1	
Metastases to central nervous			

system			
subjects affected / exposed	0 / 160 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 160 (0.63%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 2	
Renal cancer			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholesteatoma			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Deep vein thrombosis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Pneumonectomy			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
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	4 / 160 (2.50%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	1 / 160 (0.63%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain			
subjects affected / exposed	0 / 160 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 160 (1.25%)	5 / 159 (3.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 160 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 160 (0.63%)	4 / 159 (2.52%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	9 / 160 (5.63%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 10	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumothorax			
subjects affected / exposed	3 / 160 (1.88%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	6 / 160 (3.75%)	5 / 159 (3.14%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 160 (1.25%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood sodium decreased			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (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			
Foreign body aspiration			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower limb fracture			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin laceration			

subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 160 (1.25%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 160 (0.63%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Aphasia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 160 (0.63%)	5 / 159 (3.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dystonia			

subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic cerebral infarction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 160 (0.63%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorder			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraneoplastic encephalomyelitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			

subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 160 (0.63%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral disorder			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			

subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoid tissue hyperplasia			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular degeneration			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 160 (1.25%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	11 / 160 (6.88%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	11 / 12	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	3 / 160 (1.88%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 160 (0.63%)	3 / 159 (1.89%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Hepatic haemorrhage			

subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intertrigo			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain of skin			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seborrhoeic dermatitis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 160 (1.88%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus bladder			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Urinary tract obstruction			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Cushing's syndrome			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 160 (1.88%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal pain			
subjects affected / exposed	0 / 160 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 160 (1.25%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	7 / 160 (4.38%)	5 / 159 (3.14%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sepsis			
subjects affected / exposed	1 / 160 (0.63%)	4 / 159 (2.52%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin bacterial infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	2 / 160 (1.25%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 160 (0.00%)	2 / 159 (1.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine infection			
subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 160 (0.00%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 160 (1.88%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 160 (0.63%)	1 / 159 (0.63%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	1 / 160 (0.63%)	0 / 159 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Afatinib	Gefitinib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	157 / 160 (98.13%)	159 / 159 (100.00%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 160 (13.13%)	22 / 159 (13.84%)	
occurrences (all)	35	32	
Chest pain			
subjects affected / exposed	20 / 160 (12.50%)	19 / 159 (11.95%)	
occurrences (all)	26	20	
Fatigue			
subjects affected / exposed	34 / 160 (21.25%)	30 / 159 (18.87%)	
occurrences (all)	37	38	
Influenza like illness			
subjects affected / exposed	3 / 160 (1.88%)	8 / 159 (5.03%)	
occurrences (all)	3	10	
Mucosal inflammation			
subjects affected / exposed	32 / 160 (20.00%)	19 / 159 (11.95%)	
occurrences (all)	54	26	
Oedema peripheral			
subjects affected / exposed	11 / 160 (6.88%)	10 / 159 (6.29%)	
occurrences (all)	12	11	
Pyrexia			
subjects affected / exposed	22 / 160 (13.75%)	10 / 159 (6.29%)	
occurrences (all)	35	10	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	48 / 160 (30.00%)	47 / 159 (29.56%)	
occurrences (all)	60	64	
Dysphonia			
subjects affected / exposed	10 / 160 (6.25%)	5 / 159 (3.14%)	
occurrences (all)	10	5	
Dyspnoea			
subjects affected / exposed	34 / 160 (21.25%)	26 / 159 (16.35%)	
occurrences (all)	46	31	
Epistaxis			
subjects affected / exposed	30 / 160 (18.75%)	14 / 159 (8.81%)	
occurrences (all)	39	16	
Haemoptysis			
subjects affected / exposed	5 / 160 (3.13%)	9 / 159 (5.66%)	
occurrences (all)	8	10	
Nasal dryness			
subjects affected / exposed	12 / 160 (7.50%)	0 / 159 (0.00%)	
occurrences (all)	12	0	
Nasal inflammation			
subjects affected / exposed	11 / 160 (6.88%)	1 / 159 (0.63%)	
occurrences (all)	13	1	
Oropharyngeal pain			
subjects affected / exposed	7 / 160 (4.38%)	10 / 159 (6.29%)	
occurrences (all)	13	11	
Productive cough			
subjects affected / exposed	6 / 160 (3.75%)	11 / 159 (6.92%)	
occurrences (all)	17	13	
Rhinorrhoea			
subjects affected / exposed	24 / 160 (15.00%)	12 / 159 (7.55%)	
occurrences (all)	33	17	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 160 (8.13%)	9 / 159 (5.66%)	
occurrences (all)	16	11	
Anxiety			
subjects affected / exposed	4 / 160 (2.50%)	8 / 159 (5.03%)	
occurrences (all)	4	8	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 160 (11.88%)	44 / 159 (27.67%)	
occurrences (all)	27	70	
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 160 (9.38%)	38 / 159 (23.90%)	
occurrences (all)	19	57	
Weight decreased			
subjects affected / exposed	18 / 160 (11.25%)	9 / 159 (5.66%)	
occurrences (all)	19	11	
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 160 (7.50%)	18 / 159 (11.32%)	
occurrences (all)	19	22	
Headache			
subjects affected / exposed	14 / 160 (8.75%)	22 / 159 (13.84%)	
occurrences (all)	21	30	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 160 (8.75%)	5 / 159 (3.14%)	
occurrences (all)	16	6	
Eye disorders			
Dry eye			
subjects affected / exposed	15 / 160 (9.38%)	13 / 159 (8.18%)	
occurrences (all)	16	14	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 160 (8.75%)	11 / 159 (6.92%)	
occurrences (all)	16	12	
Abdominal pain upper			
subjects affected / exposed	17 / 160 (10.63%)	17 / 159 (10.69%)	
occurrences (all)	26	18	
Constipation			
subjects affected / exposed	29 / 160 (18.13%)	24 / 159 (15.09%)	
occurrences (all)	33	28	
Diarrhoea			

subjects affected / exposed	143 / 160 (89.38%)	102 / 159 (64.15%)	
occurrences (all)	451	237	
Dry mouth			
subjects affected / exposed	11 / 160 (6.88%)	14 / 159 (8.81%)	
occurrences (all)	11	14	
Dyspepsia			
subjects affected / exposed	16 / 160 (10.00%)	14 / 159 (8.81%)	
occurrences (all)	24	19	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 160 (3.75%)	13 / 159 (8.18%)	
occurrences (all)	7	13	
Mouth ulceration			
subjects affected / exposed	20 / 160 (12.50%)	7 / 159 (4.40%)	
occurrences (all)	22	7	
Nausea			
subjects affected / exposed	43 / 160 (26.88%)	45 / 159 (28.30%)	
occurrences (all)	69	55	
Stomatitis			
subjects affected / exposed	63 / 160 (39.38%)	18 / 159 (11.32%)	
occurrences (all)	106	25	
Vomiting			
subjects affected / exposed	31 / 160 (19.38%)	19 / 159 (11.95%)	
occurrences (all)	37	22	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	5 / 160 (3.13%)	17 / 159 (10.69%)	
occurrences (all)	7	23	
Alopecia			
subjects affected / exposed	19 / 160 (11.88%)	27 / 159 (16.98%)	
occurrences (all)	19	28	
Dermatitis acneiform			
subjects affected / exposed	34 / 160 (21.25%)	34 / 159 (21.38%)	
occurrences (all)	43	45	
Dry skin			
subjects affected / exposed	52 / 160 (32.50%)	63 / 159 (39.62%)	
occurrences (all)	61	72	

Erythema			
subjects affected / exposed	10 / 160 (6.25%)	4 / 159 (2.52%)	
occurrences (all)	12	5	
Nail disorder			
subjects affected / exposed	10 / 160 (6.25%)	3 / 159 (1.89%)	
occurrences (all)	10	3	
Pruritus			
subjects affected / exposed	40 / 160 (25.00%)	40 / 159 (25.16%)	
occurrences (all)	54	67	
Rash			
subjects affected / exposed	100 / 160 (62.50%)	87 / 159 (54.72%)	
occurrences (all)	187	139	
Skin fissures			
subjects affected / exposed	23 / 160 (14.38%)	6 / 159 (3.77%)	
occurrences (all)	26	7	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	7 / 160 (4.38%)	9 / 159 (5.66%)	
occurrences (all)	7	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 160 (6.88%)	16 / 159 (10.06%)	
occurrences (all)	12	21	
Back pain			
subjects affected / exposed	22 / 160 (13.75%)	32 / 159 (20.13%)	
occurrences (all)	25	45	
Muscle spasms			
subjects affected / exposed	13 / 160 (8.13%)	12 / 159 (7.55%)	
occurrences (all)	15	13	
Musculoskeletal chest pain			
subjects affected / exposed	9 / 160 (5.63%)	13 / 159 (8.18%)	
occurrences (all)	11	20	
Musculoskeletal pain			
subjects affected / exposed	14 / 160 (8.75%)	17 / 159 (10.69%)	
occurrences (all)	16	20	
Neck pain			

subjects affected / exposed	3 / 160 (1.88%)	12 / 159 (7.55%)	
occurrences (all)	3	12	
Pain in extremity			
subjects affected / exposed	20 / 160 (12.50%)	10 / 159 (6.29%)	
occurrences (all)	21	15	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	14 / 160 (8.75%)	10 / 159 (6.29%)	
occurrences (all)	18	12	
Folliculitis			
subjects affected / exposed	10 / 160 (6.25%)	4 / 159 (2.52%)	
occurrences (all)	14	4	
Nasopharyngitis			
subjects affected / exposed	11 / 160 (6.88%)	11 / 159 (6.92%)	
occurrences (all)	14	14	
Paronychia			
subjects affected / exposed	89 / 160 (55.63%)	28 / 159 (17.61%)	
occurrences (all)	136	34	
Upper respiratory tract infection			
subjects affected / exposed	16 / 160 (10.00%)	20 / 159 (12.58%)	
occurrences (all)	24	27	
Urinary tract infection			
subjects affected / exposed	18 / 160 (11.25%)	9 / 159 (5.66%)	
occurrences (all)	25	9	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	45 / 160 (28.13%)	39 / 159 (24.53%)	
occurrences (all)	69	49	
Hypokalaemia			
subjects affected / exposed	15 / 160 (9.38%)	7 / 159 (4.40%)	
occurrences (all)	22	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2011	The amendment introduced a change to the flow chart, for clarification of the informed consent process. Further major changes were the implementation of a new adverse event reporting process according to corporate Standard Operation Procedures of the sponsor, addition that afatinib is to be taken without food, and clarification on the archiving of tumour images.
11 September 2012	The amendment introduced changes to the flow chart to clarify time windows for certain procedures. The latest guidance on concomitant use of P-glycoprotein inhibitors and inducers in studies investigating afatinib was added. Further major additions concerned the management of the adverse events (AEs) diarrhoea, interstitial lung disease, and mucositis; drug induced liver injury monitoring; and reporting of sponsor-defined 'always serious AEs'. The afatinib dispersion method was changed, and reporting of progressive disease (PD) without signs or symptoms of PD was corrected.
06 March 2013	With this amendment, the text for the trial objectives was revised to have a clear distinction between end points and objectives. Regions were added to the competitive recruitment strategy, i.e. screening was competitive within two regions (Asian versus non-Asian countries), to ensure balanced ethnic composition of the trial population. With the introduction of this requirement, the sample size needed to be increased to 316 patients. The statistical section of the clinical trial protocol was revised to implement these changes; this included further details on statistical tests. A two-sided nominal alpha-level of 0.05 was prespecified for all statistical tests. Overall survival and 'time to treatment failure' changed from secondary to primary end points. The change was made to distinguish the end points considered to be of most clinical importance from the other, less important secondary end points. The time point for the primary progression-free survival (PFS) analysis readout was set as the time when at least 250 PFS events have accrued. Central imaging was added to the evaluation of tumour response. Further modifications were an amendment of the definition for end of trial, the introduction section on continued access to study treatment after study completion, and the introduction of paragraph on the management of keratitis. The reporting rules for progressive disease as an adverse event were changed.
29 July 2015	As it was estimated that overall survival (OS) data would be immature at the primary analysis time point, an additional time point for the analysis of mature OS data was defined. This time point was defined as the time when approximately two thirds of OS events (213 events) have occurred, and patients still alive and being followed up for OS have been so for at least 32 months from the date of randomisation.
20 July 2017	For patients continuing in the study, the frequency of imaging assessments was reduced after overall survival (OS) analysis. Assessments were now to be performed every 18 weeks. More frequent assessments were no longer required as patients had been on treatment for more than 3 years. Central independent review of tumour imaging was stopped after database lock for the analysis of OS. As sufficient data had been collected for the primary analysis and additional OS analysis, the definition of end of trial was changed to allow earlier completion of the trial. The frequency of electrocardiogram assessments and echocardiogram/multiple-gated acquisition scans was changed to "as clinically indicated". Completion of Quality of Life questionnaires was no longer requested after database lock for the analysis of OS as sufficient data had been collected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported