Clinical trial results:
LUX-Head & Neck 2 - A randomised, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of afatinib (BIBW 2992) as adjuvant therapy after chemo-radiotherapy in primary unresected patients with stage III, IVa, or IVb loco-regionally advanced head and neck squamous cell carcinoma.

Summary

EudraCT number	2011-000392-14
Trial protocol	GB ES BE FR NL DE FI GR AT SE IT CZ DK PT HU PL
Global end of trial date	12 September 2016

Results information

Result version number	v1
This version publication date	20 September 2017
First version publication date	20 September 2017

Trial information

Trial identification

Sponsor protocol code	1200.131

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01345669
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	25 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 September 2016
Global end of trial reached?	Yes
Global end of trial date	12 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective was to investigate the efficacy and safety of afatinib over placebo when given as adjuvant therapy after chemo-radiotherapy (CRT) in primary unresected patients with loco-regionally advanced squamous cell carcinomas (LA SCC) stage III or IVa/b of the oral cavity, oropharynx, or hypopharynx, or larynx stage IVa/b with high or intermediate risk of recurrence. The main objective of the trial was to test the superiority of afatinib as adjuvant therapy vs. placebo in terms of disease-free survival (DFS) for this trial patient population.

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 tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Belgium: 29
Country: Number of subjects enrolled	Brazil: 71
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	Chile: 10
Country: Number of subjects enrolled	Czech Republic: 22
Country: Number of subjects enrolled	Denmark: 5
Country: Number of subjects enrolled	Egypt: 2
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 65
Country: Number of subjects enrolled	Germany: 28
Country: Number of subjects enrolled	Greece: 21
Country: Number of subjects enrolled	Hungary: 22

Country: Number of subjects enrolled	India: 37
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Japan: 86
Country: Number of subjects enrolled	Mexico: 2
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Portugal: 43
Country: Number of subjects enrolled	Russian Federation: 54
Country: Number of subjects enrolled	Spain: 91
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Ukraine: 5
Country: Number of subjects enrolled	United Kingdom: 60
Country: Number of subjects enrolled	United States: 50
Worldwide total number of subjects	799
EEA total number of subjects	435

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)	603
From 65 to 84 years	196
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomised, placebo-controlled, double-blind, parallel arms, multinational phase III trial in which patients were randomised 2:1 to Afatinib or Placebo.

Pre-assignment

Screening details:

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

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Afatinib (BIBW 2992)

Arm description:

Patient received Afatinib film-coated tablets with starting dose 40 mg (milligram)/day and escalation to 50 mg/day and/or reduction to 40, 30 or 20 mg/day according to absence or presence of drug-related adverse events (AEs), orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason necessitating withdrawal.

Arm type	Experimental
Investigational medicinal product name	Afatinib (BIBW 2992)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Afatinib film-coated tablets with starting dose 40 mg (milligram)/day and escalation to 50 mg/day and/or reduction to 40, 30 or 20 mg/day according to absence or presence of drug-related adverse events (AEs), orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason (patients were discontinued after the trial was stopped prematurely by the DMC due to futility) necessitating withdrawal.

Arm title	Placebo

Arm description:

Patient received placebo matching Afatinib film-coated tablets with matching Afatinib dosage regimen, orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason necessitating withdrawal.

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

Dosage and administration details:

Placebo matching Afatinib film-coated tablets with matching Afatinib dosage regimen, orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason (patients were discontinued after the trial was stopped prematurely by the DMC due to futility) necessitating withdrawal.

Number of subjects in period 1[1]	Afatinib (BIBW 2992)	Placebo
Started	411	206
Completed	124	87
Not completed	287	119
Consent withdrawn by subject	52	13
Adverse event, non-fatal	63	9
Other Reasons	111	60
Second primary tumour	4	3
Lost to follow-up	1	1
Primary tumour recurrence	53	32
Protocol deviation	3	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on the patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	Afatinib (BIBW 2992)
Reporting group description:	
Patient received Afatinib film-coated tablets with starting dose 40 mg (milligram)/day and escalation to 50 mg/day and/or reduction to 40, 30 or 20 mg/day according to absence or presence of drug-related adverse events (AEs), orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason necessitating withdrawal.	
Reporting group title	Placebo
Reporting group description:	
Patient received placebo matching Afatinib film-coated tablets with matching Afatinib dosage regimen, orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason necessitating withdrawal.	

Reporting group values	Afatinib (BIBW 2992)	Placebo	Total
Number of subjects	411	206	617
Age categorical			
Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised)			
Units: Subjects			
Age Continuous			
Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised)			
Units: years			
arithmetic mean	58.3	57.3	
standard deviation	± 8.23	± 8.64	-
Gender, Male/Female			
Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised)			
Units: Subjects			
Female	61	28	89
Male	350	178	528

End points

End points reporting groups

Reporting group title	Afatinib (BIBW 2992)

Reporting group description:

Patient received Afatinib film-coated tablets with starting dose 40 mg (milligram)/day and escalation to 50 mg/day and/or reduction to 40, 30 or 20 mg/day according to absence or presence of drug-related adverse events (AEs), orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason necessitating withdrawal.

Reporting group title	Placebo

Reporting group description:

Patient received placebo matching Afatinib film-coated tablets with matching Afatinib dosage regimen, orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason necessitating withdrawal.

Primary: Disease Free Survival (DFS)

End point title	Disease Free Survival (DFS)

End point description:

Disease Free Survival defined as the time from randomisation until documented tumour recurrence/SPT or death from any cause, whichever occurred first. Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised). 99999: Non calculable because median or 75th percentile hasn't been reached. It is calculated when approximately 40% of the events had occurred.

End point type	Primary

End point timeframe:

Up to 5 years

End point values	Afatinib (BIBW 2992)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411[1]	206[2]		
Units: Months				
median (inter-quartile range (Q1-Q3))	43.4 (16.82 to 99999)	99999 (16.69 to 99999)		

Notes:

[1] - RS

[2] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

DFS was analysed using a stratified log-rank test with nodal status (N0- N2a vs. N2b-N3) and ECOG performance status (0 vs. 1) being the stratification factors.

Comparison groups	Afatinib (BIBW 2992) v Placebo

Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.4806
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.126
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.809
upper limit	1.569

Notes:

[3] - Hazard ratio (Afatinib vs. Placebo) from Cox proportional hazards model stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Secondary: Disease Free Survival (DFS) rate at 2 years

End point title	Disease Free Survival (DFS) rate at 2 years

End point description:

Disease Free Survival (DFS) rate at 2 years. Probability of being disease free at 2 years in percentage is provided based on Kaplan-Meier method. Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised).

End point type	Secondary

End point timeframe:

Up to 2 years

End point values	Afatinib (BIBW 2992)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117[4]	76[5]		
Units: Probability (%)				
number (confidence interval 95%)	67.2 (61.2 to 72.5)	73.5 (66 to 79.5)		

Notes:

[4] - RS

[5] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Kaplan-Meier (KM) curves were calculated for each treatment group, separately, and the estimates of DFS probabilities from the curves and 95% CI (using the Greenwood standard error estimate) were tabulated

Comparison groups	Afatinib (BIBW 2992) v Placebo

Number of subjects included in analysis	193
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.161
Method	Logrank
Parameter estimate	Difference in Kaplan-Meier estimates
Point estimate	-6.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.04
upper limit	2.5

Notes:

[6] - Difference in Kaplan-Meier estimates of Afatinib vs. Placebo is provided.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS), defined as the time from randomisation until death (regardless of cause). Due to the small event rate in both treatment arms caused by the early termination of the trial, the hazard estimate is not interpretable. Hence presented the total randomized and the percentage of patients died. Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised).

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Afatinib (BIBW 2992)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411[7]	206[8]		
Units: Percentage death events				
number (not applicable)	15.1	11.2		

Notes:

[7] - RS

[8] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratio from Cox proportional hazards model stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Comparison groups	Afatinib (BIBW 2992) v Placebo

Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1301 [9]
Method	Logrank
Parameter estimate	Odds ratio (OR)
Point estimate	1.444
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.895
upper limit	2.332

Notes:

[9] - p−value (two−sided) from log−rank test stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Secondary: Patients with improved Health Related Quality of Life (HRQOL)

End point title	Patients with improved Health Related Quality of Life (HRQOL)

End point description:

HRQoL questionnaires focused on 3 scales: Pain scale from H&N35, Swallowing scale from H&N35 and Global health status/QoL scale from C30. Improvement was defined as a score that improved from baseline by at least 10 points (on the 0-100 point scale) at any time during the study. If a patient had not improved, worsening was defined as a 10-point worsening at any time during the study. Patients who had neither improved nor worsened were considered as stable. Percentages of patients with improvement in HRQoL are presented. Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised)

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Afatinib (BIBW 2992)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411[10]	206[11]		
Units: Percentage of Patients				
number (not applicable)				
Swallowing (Q5−Q8 from QLQ−HN35)	34.8	27.2		
Pain HN35 (Q1−Q4 from QLQ−HN35)	33.8	26.2		
Global health status/QoL(Q29−Q30 from QLQ−C30)	33.6	38.3		

Notes:

[10] - RS

[11] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Odds ratio and p−value from logistic regression analysis of 'improved vs. not improved' stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3) for Swallowing (Q5−Q8 from QLQ−HN35).

Comparison groups	Afatinib (BIBW 2992) v Placebo

Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0561
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.431
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.991
upper limit	2.068

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Odds ratio and p−value from logistic regression analysis of 'improved vs. not improved' stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3) for Pain HN35 (Q1−Q4 from QLQ−HN35).

Comparison groups	Afatinib (BIBW 2992) v Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0523
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.446
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.996
upper limit	2.098

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Odds ratio and p−value from logistic regression analysis of 'improved vs. not improved' stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3) for Global health status/QoL(Q29−Q30 from QLQ−C30).

Comparison groups	Afatinib (BIBW 2992) v Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.257
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.818

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.557
upper limit	1.158

Secondary: Time to deterioration in Health Related Quality of Life (HRQOL)

End point title	Time to deterioration in Health Related Quality of Life (HRQOL)

End point description:

HRQoL questionnaires focused on 3 scales: Pain scale from H&N35, Swallowing scale from H&N35 and Global health status/QoL scale from C30. Time to deterioration was defined as the time from randomisation to the first 10-point worsening on the 0-100 point scale. Patients with no deterioration (including those with disease recurrence/SPT) were censored at the last available HRQoL assessment date. Patients with no post-baseline assessments were censored on the day of randomisation. Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised). 99999: Non calculable because 75th percentile hasn't been reached.

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Afatinib (BIBW 2992)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411[12]	206[13]		
Units: Months				
median (inter-quartile range (Q1-Q3))				
Swallowing (N=174, 74)	18.43 (3.68 to 99999)	31.44 (3.78 to 99999)		
Pain HN35 (N=185, 76)	12.06 (1.91 to 99999)	31.08 (3.78 to 99999)		
Global health status/QoL(N=205, 81)	7.59 (1.87 to 99999)	25.79 (6.21 to 99999)		

Notes:

[12] - RS

[13] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

For swallowing scale; Hazard ratio from Cox proportional hazard model stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Comparison groups	Afatinib (BIBW 2992) v Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0591 [14]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.295

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.986
upper limit	1.7

Notes:

[14] - P−value from log−rank test stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

For pain HN35 scale; Hazard ratio from Cox proportional hazard model stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Comparison groups	Afatinib (BIBW 2992) v Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0049 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.456
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.113
upper limit	1.905

Notes:

[15] - P−value from log−rank test stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

For global health status/QoL scale; Hazard ratio from Cox proportional hazard model stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Comparison groups	Afatinib (BIBW 2992) v Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002 [16]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.604
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.238
upper limit	2.079

Notes:

[16] - P−value from log−rank test stratified by baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Secondary: Health Related Quality of Life (HRQOL) scores over time

End point title	Health Related Quality of Life (HRQOL) scores over time

End point description:

HRQoL questionnaires focused on 3 scales: Pain scale from H&N35, Swallowing scale from H&N35 and Global health status/QoL scale from C30. Scoring of the symptom scales/items followed the European Organisation for Research and Treatment of Cancer (EORTC) scoring manual and a linear transformation of the scores to a 0-100 point scale. Randomised Set (RS): Included all patients who were randomised, regardless of taking investigational treatment (as randomised)

End point type	Secondary

End point timeframe:

Up to 5 years

End point values	Afatinib (BIBW 2992)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	411[17]	206[18]		
Units: Unit on Scale				
least squares mean (standard error)				
Swallowing (N=397, 196)	10.1 (± 1)	8.8 (± 1.12)		
Pain HN35 (N=397, 195)	13.1 (± 0.98)	9.9 (± 1.1)		
Global health status/QoL(N=392, 194)	29.6 (± 2.23)	33 (± 2.28)		

Notes:

[17] - RS

[18] - RS

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Scores (swallowing scale) over time were assessed using longitudinal mixed-effects growth curve models with the average profile over time for each endpoint described by a piecewise linear model adjusted for the fixed effects baseline ECOG performance score and nodal status.

Comparison groups	Afatinib (BIBW 2992) v Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.2232
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.81
upper limit	3.45
Variability estimate	Standard error of the mean
Dispersion value	1.08

Notes:

[19] - Degrees of freedom calculated using the Kenward-Roger method. Afatinib minus Placebo mean adjusted for total with data for baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Scores (pain scale) over time were assessed using longitudinal mixed-effects growth curve models with

the average profile over time for each endpoint described by a piecewise linear model adjusted for the fixed effects baseline ECOG performance score and nodal status.

Comparison groups	Afatinib (BIBW 2992) v Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.0028
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.12
upper limit	5.36
Variability estimate	Standard error of the mean
Dispersion value	1.08

Notes:

[20] - Degrees of freedom calculated using the Kenward-Roger method. Afatinib minus Placebo mean adjusted for total with data for baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Scores (global health/QoL) over time were assessed using longitudinal mixed-effects growth curve models with the average profile over time for each endpoint described by a piecewise linear model adjusted for the fixed effects baseline ECOG performance score and nodal status.

Comparison groups	Afatinib (BIBW 2992) v Placebo
Number of subjects included in analysis	617
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.0005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.33
upper limit	-1.49
Variability estimate	Standard error of the mean
Dispersion value	0.98

Notes:

[21] - Degrees of freedom calculated using the Kenward-Roger method. Afatinib minus Placebo mean adjusted for total with data for baseline ECOG (0 or 1) and nodal status (N0−N2a or N2b−N3).

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first drug administration until 4 weeks after the last drug administration, up to 84 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	Afatinib (BIBW 2992)
Reporting group description:	
Patient received Afatinib film-coated tablets with starting dose 40 mg (milligram)/day and escalation to 50 mg/day and/or reduction to 40, 30 or 20 mg/day according to absence or presence of drug-related adverse events (AEs), orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason necessitating withdrawal.	
Reporting group title	Placebo
Reporting group description:	
Patient received placebo matching Afatinib film-coated tablets with matching Afatinib dosage regimen, orally, once daily for up to 80 weeks or until recurrence / occurrence of second primary tumour, unacceptable side effects, or other reason necessitating withdrawal.	

Serious adverse events	Afatinib (BIBW 2992)	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	80 / 411 (19.46%)	51 / 206 (24.76%)	
number of deaths (all causes)	62	23	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	3 / 411 (0.73%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metastases to lung			
subjects affected / exposed	2 / 411 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm recurrence			
subjects affected / exposed	5 / 411 (1.22%)	3 / 206 (1.46%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Oesophageal carcinoma			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal squamous cell carcinoma			
subjects affected / exposed	2 / 411 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recurrent cancer			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (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 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypotension			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Disease recurrence			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Mucosal inflammation			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoidosis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 411 (0.49%)	3 / 206 (1.46%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	3 / 411 (0.73%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal dyspnoea			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	8 / 411 (1.95%)	8 / 206 (3.88%)	
occurrences causally related to treatment / all	0 / 8	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumothorax			
subjects affected / exposed	2 / 411 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary alveolar haemorrhage			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (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 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract oedema			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal stenosis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			

Device occlusion			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental overdose			

subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoradionecrosis			
subjects affected / exposed	2 / 411 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation fibrosis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation necrosis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft complication			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 411 (0.00%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Carotid artery thrombosis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 411 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Migraine			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures with secondary generalisation			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
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 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wernicke's encephalopathy			

subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (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	4 / 411 (0.97%)	2 / 206 (0.97%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal tear			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 411 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			

subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	2 / 411 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glossitis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (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	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
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 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis relapsing			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (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 / 411 (0.24%)	0 / 206 (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	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 411 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Groin pain			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 411 (0.00%)	3 / 206 (1.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	2 / 411 (0.49%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbuncle			

subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 411 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis of male external genital organ			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin infection			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis E			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (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	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 411 (0.24%)	5 / 206 (2.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 411 (0.00%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethritis			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (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	3 / 411 (0.73%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 411 (0.24%)	1 / 206 (0.49%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypokalaemia			
subjects affected / exposed	1 / 411 (0.24%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 411 (0.49%)	0 / 206 (0.00%)	
occurrences causally related to treatment / all	1 / 2	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 (BIBW 2992)	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	407 / 411 (99.03%)	169 / 206 (82.04%)	
Investigations			
Weight decreased			
subjects affected / exposed	67 / 411 (16.30%)	19 / 206 (9.22%)	
occurrences (all)	73	21	
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 411 (4.38%)	12 / 206 (5.83%)	
occurrences (all)	21	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 411 (2.68%)	13 / 206 (6.31%)	
occurrences (all)	13	16	
Dysgeusia			

subjects affected / exposed	34 / 411 (8.27%)	10 / 206 (4.85%)	
occurrences (all)	38	10	
Headache			
subjects affected / exposed	18 / 411 (4.38%)	12 / 206 (5.83%)	
occurrences (all)	19	15	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	23 / 411 (5.60%)	7 / 206 (3.40%)	
occurrences (all)	26	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	43 / 411 (10.46%)	23 / 206 (11.17%)	
occurrences (all)	58	29	
Fatigue			
subjects affected / exposed	61 / 411 (14.84%)	21 / 206 (10.19%)	
occurrences (all)	72	21	
Mucosal inflammation			
subjects affected / exposed	126 / 411 (30.66%)	17 / 206 (8.25%)	
occurrences (all)	178	21	
Pyrexia			
subjects affected / exposed	29 / 411 (7.06%)	7 / 206 (3.40%)	
occurrences (all)	36	8	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	21 / 411 (5.11%)	6 / 206 (2.91%)	
occurrences (all)	23	8	
Cheilitis			
subjects affected / exposed	22 / 411 (5.35%)	1 / 206 (0.49%)	
occurrences (all)	25	1	
Constipation			
subjects affected / exposed	33 / 411 (8.03%)	20 / 206 (9.71%)	
occurrences (all)	35	22	
Diarrhoea			
subjects affected / exposed	335 / 411 (81.51%)	41 / 206 (19.90%)	
occurrences (all)	826	61	
Dry mouth			

subjects affected / exposed	55 / 411 (13.38%)	25 / 206 (12.14%)	
occurrences (all)	67	28	
Dyspepsia			
subjects affected / exposed	42 / 411 (10.22%)	10 / 206 (4.85%)	
occurrences (all)	48	11	
Dysphagia			
subjects affected / exposed	48 / 411 (11.68%)	21 / 206 (10.19%)	
occurrences (all)	51	22	
Gastrooesophageal reflux disease			
subjects affected / exposed	23 / 411 (5.60%)	2 / 206 (0.97%)	
occurrences (all)	23	2	
Nausea			
subjects affected / exposed	43 / 411 (10.46%)	24 / 206 (11.65%)	
occurrences (all)	56	31	
Oral pain			
subjects affected / exposed	23 / 411 (5.60%)	6 / 206 (2.91%)	
occurrences (all)	27	6	
Stomatitis			
subjects affected / exposed	107 / 411 (26.03%)	12 / 206 (5.83%)	
occurrences (all)	149	16	
Vomiting			
subjects affected / exposed	40 / 411 (9.73%)	20 / 206 (9.71%)	
occurrences (all)	49	25	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	35 / 411 (8.52%)	30 / 206 (14.56%)	
occurrences (all)	41	36	
Dysphonia			
subjects affected / exposed	22 / 411 (5.35%)	17 / 206 (8.25%)	
occurrences (all)	24	18	
Epistaxis			
subjects affected / exposed	54 / 411 (13.14%)	3 / 206 (1.46%)	
occurrences (all)	74	3	
Oropharyngeal pain			

subjects affected / exposed	27 / 411 (6.57%)	14 / 206 (6.80%)	
occurrences (all)	28	14	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	22 / 411 (5.35%)	2 / 206 (0.97%)	
occurrences (all)	28	6	
Dermatitis acneiform			
subjects affected / exposed	112 / 411 (27.25%)	6 / 206 (2.91%)	
occurrences (all)	154	6	
Dry skin			
subjects affected / exposed	76 / 411 (18.49%)	16 / 206 (7.77%)	
occurrences (all)	85	18	
Erythema			
subjects affected / exposed	28 / 411 (6.81%)	5 / 206 (2.43%)	
occurrences (all)	35	5	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	30 / 411 (7.30%)	0 / 206 (0.00%)	
occurrences (all)	32	0	
Pruritus			
subjects affected / exposed	58 / 411 (14.11%)	13 / 206 (6.31%)	
occurrences (all)	77	15	
Rash			
subjects affected / exposed	188 / 411 (45.74%)	34 / 206 (16.50%)	
occurrences (all)	310	45	
Skin fissures			
subjects affected / exposed	40 / 411 (9.73%)	1 / 206 (0.49%)	
occurrences (all)	56	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 411 (2.43%)	12 / 206 (5.83%)	
occurrences (all)	11	13	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	13 / 411 (3.16%)	17 / 206 (8.25%)	
occurrences (all)	14	20	
Muscle spasms			

subjects affected / exposed	26 / 411 (6.33%)	9 / 206 (4.37%)	
occurrences (all)	37	9	
Neck pain			
subjects affected / exposed	11 / 411 (2.68%)	11 / 206 (5.34%)	
occurrences (all)	12	13	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	21 / 411 (5.11%)	2 / 206 (0.97%)	
occurrences (all)	27	4	
Nasopharyngitis			
subjects affected / exposed	22 / 411 (5.35%)	18 / 206 (8.74%)	
occurrences (all)	25	20	
Paronychia			
subjects affected / exposed	85 / 411 (20.68%)	4 / 206 (1.94%)	
occurrences (all)	105	4	
Upper respiratory tract infection			
subjects affected / exposed	19 / 411 (4.62%)	15 / 206 (7.28%)	
occurrences (all)	23	25	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	74 / 411 (18.00%)	23 / 206 (11.17%)	
occurrences (all)	87	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2011	With the introduction of this amendment, in addition to some clarifications and minor changes in study definitions, or revisions for consistency or to avoid repetitions, the following changes were made. The start of treatment was amended to start as soon as possible after randomisation and preferably on the day of randomisation. Also, tumour recurrence was changed to tumour recurrence/SPT to take into consideration that not all new tumours would be recurrence of previous tumours. Definitions for the evaluation of DILI were added. The central review procedure for imaging data for tumour assessments was clarified.
28 June 2012	With the introduction of this amendment, in addition to some clarifications and minor changes in study definitions, or revisions for consistency or to avoid repetitions, the following changes were made. Patients were eligible if CRT had been completed no longer than 24 weeks before randomisation to allow potential patients to recover from side effects induced by prior CRT, and to allow more time to perform neck dissection after CRT. The definition of NED was further clarified to provide recommendations for the assessment of lymph nodes. The first exclusion criteria (simultaneous HNSCC primaries) was removed. In the primary analysis of DFS, it was clarified that the 2 stratification factors would be included in the Cox model as strata and not as covariates. Sensitivity analyses of the primary endpoint were defined.
11 February 2014	With the introduction of this amendment, in addition to some clarifications and minor changes in study definitions, revisions for consistency or to avoid repetitions, or updates in the afatinib drug profile, the following changes were made. The best response to subsequent anticancer therapy was to be collected. Following a change in sponsor guidelines, after the first FUV (FUV1), SAEs and AESIs were to be reported if considered relevant by the investigator (signs and symptoms of recurrence/SPT were reported until recurrence/SPT had been radiologically confirmed). It was clarified that that neck dissection was allowed prior to CRT as neck dissection is not regarded as tumour resection and thus the overall patient population (primary unresected HNSCC) remained the same. Also, recognising that a patient may need longer time to recover before resuming treatment, patients who had not recovered within 21 days did not have to be discontinued. Instead, it was recommended that study medication be restarted as soon as clinically possible and within 21 days. The reporting period for AEs was clarified due to new guidelines for AE reporting. Due to extended recruitment, the text was revised to show that the first patients in the study would be followed for approximately 6 years rather than 4 years. The planned number of centres was increased from approximately 100 to approximately 200.
17 July 2015	With the introduction of this amendment, in addition to some clarifications and minor changes in study definitions, revisions for consistency or to avoid repetitions, or updating the drug profile for afatinib, the following changes were made. Further endpoints were added (time to loco-regional failure; time to distant failure; occurrence of SPTs). Some details of the primary analysis were revised, and it was to be conducted when approximately 309 patients had tumour recurrence/SPT or died (rather than when 408 patients had tumour recurrence/SPTs or died). The sample size calculation was revised to account for recently published data. It was clarified that since patients were considered having NED at randomisation, samples for biomarker analyses were typically those collected at diagnosis. The definition of DILI was revised following introduction of a new guideline.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The trial was stopped prematurely due to futility. At that point, 27.7% of patients in the study discontinued study medication prematurely due to study stop.

Notes: