



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)

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|---|-----------------------------|
| 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 occurrences (all) | 34 / 411 (8.27%) 38 | 10 / 206 (4.85%) 10 | |
| Headache subjects affected / exposed occurrences (all) | 18 / 411 (4.38%) 19 | 12 / 206 (5.83%) 15 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 23 / 411 (5.60%) 26 | 7 / 206 (3.40%) 9 | |
| General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) | 43 / 411 (10.46%) 58 | 23 / 206 (11.17%) 29 | |
| Fatigue subjects affected / exposed occurrences (all) | 61 / 411 (14.84%) 72 | 21 / 206 (10.19%) 21 | |
| Mucosal inflammation subjects affected / exposed occurrences (all) | 126 / 411 (30.66%) 178 | 17 / 206 (8.25%) 21 | |
| Pyrexia subjects affected / exposed occurrences (all) | 29 / 411 (7.06%) 36 | 7 / 206 (3.40%) 8 | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 21 / 411 (5.11%) 23 | 6 / 206 (2.91%) 8 | |
| Cheilitis subjects affected / exposed occurrences (all) | 22 / 411 (5.35%) 25 | 1 / 206 (0.49%) 1 | |
| Constipation subjects affected / exposed occurrences (all) | 33 / 411 (8.03%) 35 | 20 / 206 (9.71%) 22 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 335 / 411 (81.51%) 826 | 41 / 206 (19.90%) 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 occurrences (all) | 27 / 411 (6.57%) 28 | 14 / 206 (6.80%) 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 erythrodysesthesia 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 occurrences (all) | 26 / 411 (6.33%) 37 | 9 / 206 (4.37%) 9 | |
| Neck pain subjects affected / exposed occurrences (all) | 11 / 411 (2.68%) 12 | 11 / 206 (5.34%) 13 | |
| Infections and infestations | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 21 / 411 (5.11%) 27 | 2 / 206 (0.97%) 4 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 22 / 411 (5.35%) 25 | 18 / 206 (8.74%) 20 | |
| Paronychia subjects affected / exposed occurrences (all) | 85 / 411 (20.68%) 105 | 4 / 206 (1.94%) 4 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 19 / 411 (4.62%) 23 | 15 / 206 (7.28%) 25 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 74 / 411 (18.00%) 87 | 23 / 206 (11.17%) 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: