



Clinical trial results:

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

Summary

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

Results information

| | |
|--------------------------------|------------------|
| Result version number | v2 (current) |
| This version publication date | 14 November 2021 |
| First version publication date | 11 April 2020 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 1200.123 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01466660 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Boehringer Ingelheim |
| Sponsor organisation address | Binger Strasse 173, Ingelheim am Rhein, Germany, 55216 |
| Public contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact | QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 May 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 April 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 13 December 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Country: Number of subjects enrolled | Australia: 33 |
| Country: Number of subjects enrolled | Canada: 92 |
| Country: Number of subjects enrolled | Germany: 15 |
| Country: Number of subjects enrolled | Spain: 93 |
| Country: Number of subjects enrolled | France: 56 |
| Country: Number of subjects enrolled | Hong Kong: 6 |
| Country: Number of subjects enrolled | Ireland: 12 |
| Country: Number of subjects enrolled | Norway: 3 |
| Country: Number of subjects enrolled | China: 63 |
| Country: Number of subjects enrolled | Taiwan: 26 |
| Country: Number of subjects enrolled | Korea, Republic of: 89 |
| Country: Number of subjects enrolled | Sweden: 40 |
| Country: Number of subjects enrolled | Singapore: 31 |
| Worldwide total number of subjects | 571 |
| EEA total number of subjects | 219 |

Notes:

| Subjects enrolled per age group | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 314 |
| From 65 to 84 years | 251 |
| 85 years and over | 6 |

Subject disposition

Recruitment

Recruitment details:

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

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

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Afatinib |

Arm description:

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

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

Dosage and administration details:

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

| | |
|------------------|-----------|
| Arm title | Gefitinib |
|------------------|-----------|

Arm description:

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

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

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

Dosage and administration details:

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

| Number of subjects in period 1^[1] | Afatinib | Gefitinib |
|---|----------|-----------|
| Started | 160 | 159 |
| Completed | 0 | 0 |
| Not completed | 160 | 159 |
| Other reason not defined above | 10 | 8 |
| Refused continuation of trial medication | 4 | 3 |
| Progressive Disease (RECIST 1.1) | 120 | 127 |
| Other adverse event | 19 | 18 |
| Worsening of underlying cancer disease | 5 | 2 |
| Protocol deviation | 2 | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 571 subjects were enrolled worldwide and thereof 252 not randomised. The remaining 319 subjects were randomised and treated.

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Overall Study |
|-----------------------|---------------|

Reporting group description:

Randomised subjects.

| Reporting group values | Overall Study | Total | |
|--|---------------|-------|--|
| Number of subjects | 319 | 319 | |
| Age categorical | | | |
| Analysis set: All randomised subjects. | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 177 | 177 | |
| From 65-84 years | 138 | 138 | |
| 85 years and over | 4 | 4 | |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 62.4 | | |
| standard deviation | ± 11.0 | - | |
| Sex: Female, Male | | | |
| Units: | | | |
| Female | 197 | 197 | |
| Male | 122 | 122 | |
| Race (NIH/OMB) | | | |
| Analysis set: All randomised subjects. | | | |
| "Unknown or Not Reported" reflects the subjects in France where race was not recorded. | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 182 | 182 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 1 | 1 | |
| White | 102 | 102 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 34 | 34 | |

End points

End points reporting groups

| | |
|--|-----------|
| Reporting group title | Afatinib |
| Reporting group description: | |
| Afatinib film-coated tablets administered orally, once daily. Starting dose was 40 milligram (mg), dose escalation to 50mg was allowed after completing one 28-day treatment course, dose reduction to 40mg, 30mg or 20mg was required in the presence of protocol-defined adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal. | |
| Reporting group title | Gefitinib |
| Reporting group description: | |
| Gefitinib film-coated tablets, administered orally, once daily. Starting dose was 250mg, the investigator was allowed to modify dosing in the presence of drug-related adverse events. Continuous daily dosing until disease progression, occurrence of unacceptable adverse events, or other reason necessitating withdrawal. | |

Primary: Progression-free survival

| | |
|---|---------------------------|
| End point title | Progression-free survival |
| End point description: | |
| Progression-free survival (PFS) defined as the time from date of randomisation to date of disease progression, or date of death if a patient died earlier. Participants with no event (Disease progression (PD) or death) were censored. PD was primarily evaluated for the primary analysis by an independent central imaging review according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Per RECIST version 1.1. for target lesions and assessed by Computed Tomography (CT)-scan or Magnetic Resonance Imaging (MRI): PD, At least a 20% increase in the sum of the longest diameter (SoD) of target lesions taking as reference the smallest SoD of target lesions recorded since the treatment started, together with an absolute increase in the SoD of target lesions of at least 5 millimetre (mm) or the appearance of one or more new lesions. For the final analysis (analysis cut-off date 12 April 2019) status and date of PD were determined by investigator assessment. | |
| End point type | Primary |
| End point timeframe: | |
| From first drug administration until 28 days after last drug administration + Follow-Up period for collecting information on disease progression or death, up to 2465 days. | |

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

Notes:

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

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

Statistical analyses

| | |
|--|------------------------|
| Statistical analysis title | Time-to-event analysis |
| Statistical analysis description: | |
| Exploratory trial, no formal hypotheses were tested. | |
| Comparison groups | Afatinib v Gefitinib |

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

Notes:

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

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

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

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

| | |
|--|------------------------------|
| Statistical analysis title | Time-to-event analysis |
| Statistical analysis description: | |
| Exploratory trial, no formal hypotheses were tested. | |
| Comparison groups | Afatinib v Gefitinib |
| Number of subjects included in analysis | 319 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | ≤ 0.0136 ^[6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |

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

Notes:

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

Primary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Time-to-event analysis |
|----------------------------|------------------------|

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

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

Notes:

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

Secondary: Objective response rate

| | |
|-----------------|-------------------------|
| End point title | Objective response rate |
|-----------------|-------------------------|

End point description:

Objective response rate (ORR) which was defined as the number of participants with best overall response of complete response (CR) or partial response (PR) as assessed by central independent review according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. divided by the total number of participants who received treatment. Per RECIST version 1.1. for target lesions and assessed by Computed Tomography (CT)-scan or Magnetic Resonance Imaging (MRI): Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions from baseline. For the final analysis (analysis cut-off date 12 April 2019) objective response was determined by investigator assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

| | |
|----------------------------|------------------------------|
| Statistical analysis title | Logistic regression analysis |
|----------------------------|------------------------------|

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

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

Notes:

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

Secondary: Time to objective response

| | |
|-----------------|----------------------------|
| End point title | Time to objective response |
|-----------------|----------------------------|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[13] - All randomised subjects with objective response.

[14] - All randomised subjects with objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of objective response

| | |
|-----------------|--------------------------------|
| End point title | Duration of objective response |
|-----------------|--------------------------------|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[15] - All randomised subjects with objective response.

[16] - All randomised subjects with objective response.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control

| | |
|-----------------|-----------------|
| End point title | Disease control |
|-----------------|-----------------|

End point description:

Percentage of participants with disease control defined as the number of participants with best overall response of complete response (CR) or partial response (PR) or stable disease (SD) as assessed by central independent review according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. divided by the total number of participants who received treatment. Per RECIST version 1.1. for target lesions and assessed by Computed Tomography (CT)-scan or Magnetic Resonance Imaging (MRI): Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions from baseline; Stable Disease (SD), Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Responses of SD were only considered if they occur ≥ 42 days from date of randomisation. For the final analysis (analysis cut-off date 12 April 2019) disease control was determined by investigator assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

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

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

Statistical analyses

| | |
|----------------------------|------------------------------|
| Statistical analysis title | Logistic regression analysis |
|----------------------------|------------------------------|

Statistical analysis description:

Exploratory trial, no formal hypotheses were tested.

| | |
|-------------------|----------------------|
| Comparison groups | Afatinib v Gefitinib |
|-------------------|----------------------|

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

Notes:

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

Secondary: Duration of disease control

| | |
|-----------------|-----------------------------|
| End point title | Duration of disease control |
|-----------------|-----------------------------|

End point description:

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

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

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

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

Notes:

[20] - All randomised subjects with disease control.

[21] - All randomised subjects with disease control.

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From first drug administration until last drug administration, up to 1482 days | |

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

Notes:

[22] - All randomised subjects with tumour assessments.

[23] - All randomised subjects with tumour assessments.

Statistical analyses

| | |
|--|--------------------------------|
| Statistical analysis title | Analysis of covariance |
| Statistical analysis description: | |
| Exploratory trial, no formal hypotheses were tested. | |
| Comparison groups | Afatinib v Gefitinib |
| Number of subjects included in analysis | 300 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | ≤ 0.0657 ^[24] |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -3.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.13 |
| upper limit | 0.23 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.87 |

Notes:

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

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

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

End point description:

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

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

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

Results display the mean score up to 56 weeks.

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

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

Notes:

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

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

Statistical analyses

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

Notes:

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

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

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

Notes:

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

| | |
|--|----------------------------------|
| Statistical analysis title | Mixed models analysis for EQ-VAS |
| Statistical analysis description: | |
| EQ-VAS utility score. Exploratory trial, no formal hypotheses were tested. | |
| Comparison groups | Afatinib v Gefitinib |
| Number of subjects included in analysis | 318 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | ≤ 0.2032 ^[29] |
| Method | Mixed models analysis |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.9 |
| upper limit | 0.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.21 |

Notes:

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first drug administration until 28 days after last drug administration, up to 2405 days.

For All-Cause Mortality: From first drug administration until 28 days after last drug administration + Follow-Up period to collect death, up to 2465 days

Adverse event reporting additional description:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Gefitinib |
|-----------------------|-----------|

Reporting group description:

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

| | |
|-----------------------|----------|
| Reporting group title | Afatinib |
|-----------------------|----------|

Reporting group description:

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

| Serious adverse events | Gefitinib | Afatinib | |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 64 / 159 (40.25%) | 75 / 160 (46.88%) | |
| number of deaths (all causes) | 132 | 126 | |
| number of deaths resulting from adverse events | 10 | 16 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 7 / 160 (4.38%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 5 | |
| Metastases to central nervous | | | |

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 2 / 160 (1.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 159 (1.26%) | 11 / 160 (6.88%) | |
| occurrences causally related to treatment / all | 1 / 2 | 11 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (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 | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 3 / 160 (1.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 159 (1.89%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 1 / 159 (0.63%) | 0 / 160 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Hepatic haemorrhage | | | |

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 159 (0.00%) | 1 / 160 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported