



## Clinical trial results:

**A phase Ib open label clinical trial of continuous once daily oral treatment using BIBW 2992 plus cetuximab (Erbix®) in patients with non-small cell lung cancer with progression following prior erlotinib (Tarceva®) or gefitinib (Iressa®)**

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

## Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2009-015911-42 |
| Trial protocol           | NL             |
| Global end of trial date | 08 August 2014 |

## Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 06 April 2016 |
| First version publication date | 06 April 2016 |

## Trial information

### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | 1200.71 |
|-----------------------|---------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01090011 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Boehringer Ingelheim  |
| Sponsor organisation address | Binger Strasse 173 , 55216 Ingelheim am Rhein , Germany,  |
| Public contact               | QRPE Processes and Systems Coordination<br>Clinical Trial Information Disclosure , Boehringer Ingelheim ,<br>+1 8002430127, clintriage.rdg@boehringer-ingelheim.com |
| Scientific contact           | QRPE Processes and Systems Coordination<br>Clinical Trial Information Disclosure , Boehringer Ingelheim ,<br>+1 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                       | 07 November 2013 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 11 January 2013  |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 08 August 2014   |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To establish the maximum tolerated dose (MTD) and recommended Phase II doses and evaluate the safety and preliminary anti-tumor activity for the combination of BIBW 2992 and cetuximab in patients with non-small cell lung cancer and acquired resistance to erlotinib, gefitinib or BIBW 2992.

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. Symptomatic treatment of tumour-associated symptoms, such as radiation therapy with palliative intent was allowed. Concomitant medications, or therapy to provide adequate supportive care, were allowed as clinically necessary. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) was required to exclude interstitial lung disease (ILD). Study drugs were to be interrupted pending investigation of these symptoms. If ILD was diagnosed, study drug was to be permanently discontinued and appropriate treatment instituted as necessary.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 26 March 2010 |
| 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 | Netherlands: 37    |
| Country: Number of subjects enrolled | United States: 164 |
| Worldwide total number of subjects   | 201                |
| EEA total number of subjects         | 37                 |

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)      | 146 |
| From 65 to 84 years       | 54  |
| 85 years and over         | 1   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects attended specialist sites which would then ensure that they (Subjects) met all inclusion/exclusion criteria. Subjects were not to be randomised to trial treatment if any one of the entry criteria were violated. Therefore 171 patients were treated in this study.

### Period 1

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 1 title               | Treatment period (overall period) |
| Is this the baseline period? | Yes                               |
| Allocation method            | Non-randomised - controlled       |
| Blinding used                | Not blinded                       |

### Arms

|                              |                               |
|------------------------------|-------------------------------|
| Are arms mutually exclusive? | No                            |
| <b>Arm title</b>             | Combination Arm -Afa40+Ctx250 |

Arm description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with Acquired Resistance (AR) to erlotinib or gefitinib)

Afatinib 40 mg + cetuximab 250 mg/m<sup>2</sup> (Afa40+Ctx250)

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | afatinib     |
| Investigational medicinal product code | BIBW 2992    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Continuous once daily oral treatment using 40 mg BIBW 2992 plus cetuximab 250 mg/m<sup>2</sup> every two weeks (q2wk) up to 28 days

|                  |                                |
|------------------|--------------------------------|
| <b>Arm title</b> | Combination Arm - Afa40+Ctx500 |
|------------------|--------------------------------|

Arm description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with AR to erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m<sup>2</sup> (Afa40+Ctx500)

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | afatinib     |
| Investigational medicinal product code | BIBW 2992    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Continuous once daily oral treatment using 40 mg BIBW 2992 plus cetuximab 500mg q2wk up to 28 days.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) |
|------------------|--|

Arm description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the Maximum Tolerated Dose (MTD) determined in the

combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

#### Afatinib 40 mg (Afa40 Mono)

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | afatinib     |
| Investigational medicinal product code | BIBW 2992    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Monotherapy afatinib daily 40 mg orally taken

|                  |   |
|------------------|---|
| <b>Arm title</b> | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|------------------|---|

Arm description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the MTD determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

#### Afatinib 40 mg + cetuximab 500 mg/m<sup>2</sup> (Afa40+Ctx500)

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | afatinib     |
| Investigational medicinal product code | BIBW 2992    |
| Other name                             |              |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Continuous once daily oral treatment using 40 mg BIBW 2992 plus cetuximab 500mg q2wk

| Number of subjects in period 1  | Combination Arm -<br>Afa40+Ctx250 | Combination Arm -<br>Afa40+Ctx500 | Sequential Arm -<br>Afatinib<br>Monotherapy (Afa40<br>Mono) |
|---------------------------------|-----------------------------------|-----------------------------------|---|
|                                 |                                   |                                   |   |
| Started                         | 4                                 | 126                               | 37  |
| Completed                       | 0                                 | 0                                 | 0   |
| Not completed                   | 4                                 | 126                               | 37  |
| Adverse event, serious fatal    | -                                 | 7                                 | 1   |
| Consent withdrawn by subject    | 1                                 | 3                                 | -   |
| Adverse event, non-fatal        | 2                                 | 16                                | -   |
| 'other reason not found above ' | -                                 | -                                 | -   |
| Progressive disease             | 1                                 | 99                                | 36  |
| Protocol deviation              | -                                 | 1                                 | -   |

| Number of subjects in period 1 | Sequential Arm -<br>Combination<br>Therapy<br>(Afa40+Ctx500) |
|--------------------------------|--|
| Started                        | 36   |
| Completed                      | 0  |
| Not completed                  | 36   |
| Adverse event, serious fatal   | 1  |

|                                 |    |
|---------------------------------|----|
| Consent withdrawn by subject    | 1  |
| Adverse event, non-fatal        | 5  |
| 'other reason not found above ' | 5  |
| Progressive disease             | 24 |
| Protocol deviation              | -  |

## Baseline characteristics

### Reporting groups<sup>[1]</sup>

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Treatment period |
|-----------------------|------------------|

|                                |
|--------------------------------|
| Reporting group description: - |
|--------------------------------|

Notes:

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

Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication.

| Reporting group values             | Treatment period | Total |  |
|------------------------------------|------------------|-------|--|
| Number of subjects                 | 171              | 171   |  |
| Age categorical<br>Units: Subjects |                  |       |  |

|  |                |     |  |
|--|----------------|-----|--|
| Age continuous   |                |     |  |
| Treated set (TS): all patients who received at least one dose of afatinib+ cetuximab following afatinib monotherapy were included in the analysis. |                |     |  |
| Units: years<br>arithmetic mean<br>standard deviation  | 58.1<br>± 10.5 | -   |  |
| Gender categorical<br>Units: Subjects  |                |     |  |
| Female   | 119            | 119 |  |
| Male   | 52             | 52  |  |

## End points

### End points reporting groups

|   |   |
|---|---|
| Reporting group title   | Combination Arm -Afa40+Ctx250                       |
| Reporting group description:<br>Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with Acquired Resistance (AR) to erlotinib or gefitinib)  |   |
| Afatinib 40 mg + cetuximab 250 mg/m <sup>2</sup> (Afa40+Ctx250)   |   |
| Reporting group title   | Combination Arm - Afa40+Ctx500                      |
| Reporting group description:<br>Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with AR to erlotinib or gefitinib).   |   |
| Afatinib 40 mg + cetuximab 500 mg/m <sup>2</sup> (Afa40+Ctx500)   |   |
| Reporting group title   | Sequential Arm - Afatinib Monotherapy (Afa40 Mono)  |
| Reporting group description:<br>Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the Maximum Tolerated Dose (MTD) determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib). |   |
| Afatinib 40 mg (Afa40 Mono)   |   |
| Reporting group title   | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
| Reporting group description:<br>Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the MTD determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).                          |   |
| Afatinib 40 mg + cetuximab 500 mg/m <sup>2</sup> (Afa40+Ctx500)   |   |

### Primary: The Occurrence of Dose Limiting Toxicity (DLT)

|  |  |
|--|--|
| End point title  | The Occurrence of Dose Limiting Toxicity (DLT) <sup>[1][2]</sup> |
| End point description:<br>A DLT was defined as an AE or laboratory abnormality that a) related to the study regimen; b) or met any of the following criteria: <ul style="list-style-type: none"><li>• CTCAE Grade 2 or higher decrease in cardiac left ventricular function</li><li>• CTCAE Grade 2 diarrhea lasting for 7 or more days, despite appropriate use of standard anti-diarrheal therapy</li><li>• CTCAE Grade ≥3 diarrhea despite appropriate use of standard anti-diarrheal therapy for at least 2 days</li><li>• CTCAE Grade ≥3 nausea and/or vomiting despite appropriate use of standard anti-emetics for at least 3 days</li><li>• CTCAE Grade ≥3 rash despite standard medical management</li><li>• CTCAE Grade ≥3 fatigue lasting for more than 7 days</li><li>• CTCAE Grade 4 hypomagnesaemia or Grade 3 hypomagnesaemia with clinical significant sequelae</li><li>• All other toxicities of CTCAE Grade ≥3 (except alopecia, and allergic reaction) leading to an interruption of afatinib and/or cetuximab for more than 14 days until recovery to baseline or Grade 1, whichever was higher.</li></ul> |  |
| End point type   | Primary  |
| End point timeframe:<br>from day 1 treatment until progression or undue toxicity, up to 28 days  |  |

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.



[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values            | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|-----------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type          | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed | 4 <sup>[3]</sup>               | 6 <sup>[4]</sup>               |  |  |
| Units: participants         | 0                              | 0                              |  |  |

Notes:

[3] - Treatment Set for cohort one. Cohort one is the first treatment cycle that 4 pats recieved afa+ce250

[4] - Treatment Set for cohort one. Cohort one is the first treatment cycle that 6 pats recieved afa+ce500

## Statistical analyses

No statistical analyses for this end point

## Secondary: Highest CTCAE Grade

|                 |                     |
|-----------------|---------------------|
| End point title | Highest CTCAE Grade |
|-----------------|---------------------|

End point description:

Safety of afatinib when administered together with cetuximab as indicated by intensity and incidence of adverse events, graded according to the U.S. National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Version (v) 3.0

Results were based on Treated set (TS). 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

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

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

| End point values                    | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|-------------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                  | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed         | 4 <sup>[5]</sup>               | 126 <sup>[6]</sup>             | 37 <sup>[7]</sup>                                  | 36 <sup>[8]</sup>                                   |
| Units: percentage of participants   |                                |                                |  |   |
| number (not applicable)             |                                |                                |  |   |
| Patients with highest CTCAE grade 1 | 0                              | 0.8                            | 10.8   | 2.8   |
| Patients with highest CTCAE grade 2 | 25                             | 26.2                           | 24.3   | 19.4  |
| Patients with highest CTCAE grade 3 | 50                             | 54                             | 48.6   | 52.8  |
| Patients with highest CTCAE grade 4 | 25                             | 4                              | 5.4  | 8.3   |
| Patients with highest CTCAE grade 5 | 0                              | 15.1                           | 10.8   | 16.7  |

Notes:

[5] - TS

[6] - TS

[7] - TS

[8] - TS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Frequency of Patients [N(%)] With Possible Clinically Significant Abnormalities for Selected Laboratory Parameters

|                 |  |
|-----------------|--|
| End point title | Frequency of Patients [N(%)] With Possible Clinically Significant Abnormalities for Selected Laboratory Parameters |
|-----------------|--|

End point description:

Frequency of patients [N(%)] with possible clinically significant abnormalities for haemoglobin - low, white blood cell ct. - low, neutrophils - low, sodium - low, sodium - high, potassium - low, potassium - high, calcium - low, calcium - high, magnesium - low, AST/GOT, SGOT - high, ALT/GPT, SGPT - high, alkaline phosphatase - high

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

99999=Not calculable

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

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

| End point values                           | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|--|--------------------------------|--------------------------------|--|---|
| Subject group type                         | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed                | 4 <sup>[9]</sup>               | 126 <sup>[10]</sup>            | 37 <sup>[11]</sup>                                 | 36 <sup>[12]</sup>                                  |
| Units: percentage of participants          |                                |                                |  |   |
| number (not applicable)                    |                                |                                |  |   |
| Haemoglobin - low (N=4,124,35,35)          | 0                              | 12.9                           | 20   | 2.9   |
| White blood cell ct. - low (N=4,124,35,35) | 0                              | 3.2                            | 0  | 2.9   |
| Neutrophils - low (N=4,124,35,35)          | 0                              | 4                              | 0  | 2.9   |
| Sodium - low (N=4,124,35,35)               | 0                              | 5.6                            | 0  | 2.9   |
| Sodium - high (N=4,124,35,35)              | 0                              | 0.8                            | 0  | 0   |
| Potassium - low (N=4,124,35,35)            | 0                              | 5.6                            | 2.9  | 5.7   |
| Potassium - high (N=4,124,35,35)           | 0                              | 4                              | 0  | 0   |
| Calcium - low (N=4,124,35,35)              | 0                              | 6.5                            | 8.6  | 5.7   |
| Calcium - high (N=4,124,35,35)             | 0                              | 1.6                            | 0  | 0   |
| Magnesium - low (N=4,124,34,35)            | 0                              | 9.7                            | 0  | 11.4  |
| AST/GOT, SGOT - high (N=4,123,35,35)       | 0                              | 3.3                            | 0  | 2.9   |
| ALT/GPT, SGPT - high (N=4,123,35,35)       | 0                              | 11.4                           | 0  | 8.6   |

|  |       |     |     |     |
|--|-------|-----|-----|-----|
| Alkaline phosphatase - high (N=4,124,35,35)        | 25    | 4.8 | 2.9 | 5.7 |
| Blood urea nitrogen - high (N=missing, 105, 28,28) | 99999 | 5.7 | 3.6 | 0   |
| Creatinine - high (N=4,123,33,35)                  | 0     | 2.4 | 0   | 0   |
| Creatinine clearance - low (N=4,123,33,35)         | 0     | 3.3 | 0   | 2.9 |
| Bilirubin, total - high (N=4,124,35,35)            | 0     | 4.8 | 2.9 | 5.7 |

Notes:

[9] - TS

[10] - TS

[11] - TS

[12] - TS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Frequency (%) of Patients With Adverse Events Leading to Dose Reduction

|                 |   |
|-----------------|---|
| End point title | Frequency (%) of Patients With Adverse Events Leading to Dose Reduction |
|-----------------|---|

End point description:

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

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

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

| End point values                  | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|-----------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed       | 4 <sup>[13]</sup>              | 126 <sup>[14]</sup>            | 37 <sup>[15]</sup>                                 | 36 <sup>[16]</sup>                                  |
| Units: Percentage of participants |                                |                                |  |   |
| number (not applicable)           | 25                             | 37.3                           | 13.5   | 22.2  |

Notes:

[13] - TS

[14] - TS

[15] - TS

[16] - TS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Frequency (%) of Patients With Adverse Events Leading to Treatment Discontinuation

|                 |  |
|-----------------|--|
| End point title | Frequency (%) of Patients With Adverse Events Leading to |
|-----------------|--|

## End point description:

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

## End point type

Secondary

## End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

| End point values                  | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|-----------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed       | 4 <sup>[17]</sup>              | 126 <sup>[18]</sup>            | 37 <sup>[19]</sup>                                 | 36 <sup>[20]</sup>                                  |
| Units: percentage of participants |                                |                                |  |   |
| number (not applicable)           | 50                             | 23.8                           | 2.7  | 19.4  |

Notes:

[17] - TS

[18] - TS

[19] - TS

[20] - TS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Frequency (%) of Patients With Adverse Events Leading to Death

## End point title

Frequency (%) of Patients With Adverse Events Leading to Death

## End point description:

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

## End point type

Secondary

## End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

| End point values                  | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|-----------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed       | 4 <sup>[21]</sup>              | 126 <sup>[22]</sup>            | 37 <sup>[23]</sup>                                 | 36 <sup>[24]</sup>                                  |
| Units: percentage of participants |                                |                                |  |   |
| number (not applicable)           | 0                              | 15.1                           | 10.8   | 16.7  |

Notes:

[21] - TS

[22] - TS

[23] - TS

[24] - TS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Frequency (%) of Patients With Related Serious Adverse Events

|                 |   |
|-----------------|---|
| End point title | Frequency (%) of Patients With Related Serious Adverse Events |
|-----------------|---|

End point description:

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

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

End point timeframe:

From the first drug administration to 28 days after discontinuation of drug intake up to 915 days

| End point values                  | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|-----------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed       | 4 <sup>[25]</sup>              | 126 <sup>[26]</sup>            | 37 <sup>[27]</sup>                                 | 36 <sup>[28]</sup>                                  |
| Units: percentage of participants |                                |                                |  |   |
| number (not applicable)           | 0                              | 10.3                           | 5.4  | 2.8   |

Notes:

[25] - TS

[26] - TS

[27] - TS

[28] - TS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Area Under the Concentration-time Curve (AUC) on Day 15 of Plasma Afatinib for the Combination Arm

|                 |  |
|-----------------|--|
| End point title | Area Under the Concentration-time Curve (AUC) on Day 15 of Plasma Afatinib for the Combination Arm <sup>[29]</sup> |
|-----------------|--|

End point description:

Area Under the Concentration-time Curve (AUC) of Afatinib in plasma at steady state over a uniform dosing interval tau (15 days) (AUC<sub>tau,ss</sub>) after oral administration of Afatinib and cetuximab combination therapy.

The pharmacokinetic set (PKS) consisted of all patients, who received at least one dose of afatinib or cetuximab and for whom at least one observation was available.

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

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Reporting statistics are only presented for selected arms by the protocol.

| End point values                                    | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                                  | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                         | 3 <sup>[30]</sup>              | 20 <sup>[31]</sup>             |  |  |
| Units: ng*h/mL                                      |                                |                                |  |  |
| geometric mean (geometric coefficient of variation) | 1300 (± 21.8)                  | 935 (± 59.8)                   |  |  |

Notes:

[30] - Pharmacokinetic Set (PKS)

[31] - PKS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Concentration of Afatinib in Plasma for the Combination Arm

|                 |   |
|-----------------|---|
| End point title | Concentration of Afatinib in Plasma for the Combination Arm <sup>[32]</sup> |
|-----------------|---|

End point description:

Minimum measured concentration of Afatinib in plasma at steady state over 15 day dosing interval (C<sub>min,ss</sub>). Maximum measured concentration of Afatinib in plasma at steady state over 15 day dosing interval (C<sub>max,ss</sub>).

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

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[32] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                                    | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                                  | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                         | 3 <sup>[33]</sup>              | 24 <sup>[34]</sup>             |  |  |
| Units: ng/mL  |                                |                                |  |  |
| geometric mean (geometric coefficient of variation) |                                |                                |  |  |
| C <sub>min,ss,15</sub>                              | 33.9 (± 19.6)                  | 24.4 (± 53.7)                  |  |  |
| C <sub>max,ss,15</sub>                              | 83.8 (± 19.8)                  | 52.3 (± 73.2)                  |  |  |

Notes:

[33] - PKS

[34] - PKS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Peak-trough Fluctuation (PTF)

|   |   |
|---|---|
| End point title   | Peak-trough Fluctuation (PTF) <sup>[35]</sup> |
| End point description:<br>Peak-trough fluctuation (PTF) of plasma afatinib for the combination arm. $PTF = 100 * (C_{max} - C_{min}) / C_{average}$ where $C_{average} = AUC / \text{time}$ , where time equals 24 hours. |   |
| End point type  | Secondary                                     |
| End point timeframe:<br>Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55   |   |

Notes:

[35] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                                    | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                                  | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                         | 3 <sup>[36]</sup>              | 20 <sup>[37]</sup>             |  |  |
| Units: % of average concentration                   |                                |                                |  |  |
| geometric mean (geometric coefficient of variation) | 91.6 (± 15.9)                  | 73.8 (± 55.2)                  |  |  |

Notes:

[36] - PKS

[37] - PKS

## Statistical analyses

No statistical analyses for this end point

## Secondary: t1/2,ss

|   |                         |
|---|-------------------------|
| End point title   | t1/2,ss <sup>[38]</sup> |
| End point description:<br>Terminal half-life of Afatinib in plasma at steady state (t1/2,ss)            |                         |
| Data entry = "99999" stands for missing value.  |                         |
| End point type  | Secondary               |
| End point timeframe:<br>Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55 |                         |

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                      | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|---------------------------------------|--------------------------------|--------------------------------|--|--|
| Subject group type                    | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed           | 3 <sup>[39]</sup>              | 21 <sup>[40]</sup>             |  |  |
| Units: hour                           |                                |                                |  |  |
| geometric mean (geometric coefficient | 22.4 (± 24.5)                  | 99999 (±                       |  |  |

|               |        |
|---------------|--------|
| of variation) | 99999) |
|---------------|--------|

Notes:

[39] - PKS

[40] - PKS

## Statistical analyses

No statistical analyses for this end point

### Secondary: MRTpo,ss

|                 |                          |
|-----------------|--------------------------|
| End point title | MRTpo,ss <sup>[41]</sup> |
|-----------------|--------------------------|

End point description:

Mean residence time of Afatinib in the body at steady state after oral administration (MRTpo,ss) for 15 days.

Data entry = "99999" stands for missing value.

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

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                                    | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                                  | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                         | 3 <sup>[42]</sup>              | 20 <sup>[43]</sup>             |  |  |
| Units: hour   |                                |                                |  |  |
| geometric mean (geometric coefficient of variation) | 32.6 (± 23.4)                  | 99999 (± 99999)                |  |  |

Notes:

[42] - PKS

[43] - PKS

## Statistical analyses

No statistical analyses for this end point

### Secondary: CL/F,ss,15

|                 |                            |
|-----------------|----------------------------|
| End point title | CL/F,ss,15 <sup>[44]</sup> |
|-----------------|----------------------------|

End point description:

Apparent clearance of afatinib in plasma at steady state after extravascular multiple dose administration (CL/F,ss)

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

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[44] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.



Justification: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                                    | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                                  | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                         | 3 <sup>[45]</sup>              | 20 <sup>[46]</sup>             |  |  |
| Units: mL/min                                       |                                |                                |  |  |
| geometric mean (geometric coefficient of variation) | 511 (± 21.8)                   | 713 (± 59.8)                   |  |  |

Notes:

[45] - PKS

[46] - PKS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Vz/F,ss

|                 |                         |
|-----------------|-------------------------|
| End point title | Vz/F,ss <sup>[47]</sup> |
|-----------------|-------------------------|

End point description:

Apparent volume of distribution during the terminal phase λ<sub>z</sub> at steady state following extravascular administration (Vz/F,ss) for 15 days

Data entry = "99999" stands for missing value.

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

End point timeframe:

Course 1, Visit 3 and 4, Day 15 and 16, Hours: -0:05,0,1,2,3,4,5,6,8, and 23:55

Notes:

[47] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Reporting statistics are only presented for selected arms by the protocol.

| End point values                                    | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                                  | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                         | 3 <sup>[48]</sup>              | 21 <sup>[49]</sup>             |  |  |
| Units: Liter  |                                |                                |  |  |
| geometric mean (geometric coefficient of variation) | 991 (± 44.8)                   | 99999 (± 99999)                |  |  |

Notes:

[48] - PKS

[49] - PKS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Predose Plasma Concentrations of Afatinib for the Combination Arm

|                 |   |
|-----------------|---|
| End point title | Predose Plasma Concentrations of Afatinib for the Combination Arm <sup>[50]</sup> |
|-----------------|---|

End point description:

Predose plasma concentrations (Cpre,ss) of Afatinib at Course 1, Visit 2, 3, 4 and 5, at Course 2, Visit 1 and 2 and at Course 3, Visit 1.

Data entry = "99999" stands for missing values.

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

End point timeframe:

Up to 57 days

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those arms for which the statistics are presented in the clinical trial report thus, those that would yield meaningful results were reported.

| End point values                                    | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 |  |  |
|---|--------------------------------|--------------------------------|--|--|
| Subject group type                                  | Reporting group                | Reporting group                |  |  |
| Number of subjects analysed                         | 4 <sup>[51]</sup>              | 28 <sup>[52]</sup>             |  |  |
| Units: ng/mL  |                                |                                |  |  |
| geometric mean (geometric coefficient of variation) |                                |                                |  |  |
| Cpre,ss,8 (N=4,25)                                  | 33.2 (± 38.3)                  | 28.3 (± 62.3)                  |  |  |
| Cpre,ss,15 (N=3,28)                                 | 33.9 (± 19.6)                  | 27.1 (± 51.3)                  |  |  |
| Cpre,ss,16 (N=3,0)                                  | 36.4 (± 15.8)                  | 99999 (± 99999)                |  |  |
| Cpre,ss,22 (N=3,21)                                 | 33.5 (± 1.3)                   | 28.3 (± 64.3)                  |  |  |
| Cpre,ss,29 (N=3,20)                                 | 33.4 (± 21.8)                  | 27.7 (± 56.8)                  |  |  |
| Cpre,ss,43 (N=3,19)                                 | 33.5 (± 14.9)                  | 26 (± 98.4)                    |  |  |
| Cpre,ss,57 (N=3,0)                                  | 36.6 (± 4.51)                  | 99999 (± 99999)                |  |  |

Notes:

[51] - PKS

[52] - PKS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Disease Control (CR, PR and Stable Disease (SD) Determined by RECIST v1.1)

|                 |  |
|-----------------|--|
| End point title | Disease Control (CR, PR and Stable Disease (SD) Determined by RECIST v1.1) |
|-----------------|--|

End point description:

Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) for target lesions and assessed by 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; Progressive Disease (PD), At least a 20% increase in the sum of the longest diameter of target lesions or the appearance of new lesion(s); Stable Disease (SD), Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Disease control = CR + PR + SD.

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section.

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

End point timeframe:

up to 116 weeks

| End point values                  | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|-----------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed       | 4 <sup>[53]</sup>              | 126 <sup>[54]</sup>            | 37 <sup>[55]</sup>                                 | 36 <sup>[56]</sup>                                  |
| Units: percentage of participants |                                |                                |  |   |
| number (confidence interval 95%)  | 75 (19.4 to 99.4)              | 70.6 (61.9 to 78.4)            | 56.8 (39.5 to 72.9)                                | 50 (32.9 to 67.1)                                   |

Notes:

[53] - Treated set.

[54] - TS

[55] - TS

[56] - TS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Objective Tumor Response (Complete Response [CR] and Partial Response [PR])

|                 |   |
|-----------------|---|
| End point title | Objective Tumor Response (Complete Response [CR] and Partial Response [PR]) |
|-----------------|---|

End point description:

Per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1) for target lesions and assessed by 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; Progressive Disease (PD), At least a 20% increase in the sum of the longest diameter of target lesions or the appearance of new lesion(s); Stable Disease (SD), Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Objective tumor response = CR + PR.

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

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

End point timeframe:

up to 116 weeks

| End point values                  | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|-----------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed       | 4 <sup>[57]</sup>              | 126 <sup>[58]</sup>            | 37 <sup>[59]</sup>                                 | 36 <sup>[60]</sup>                                  |
| Units: Percentage of participants |                                |                                |  |   |
| number (confidence interval 95%)  | 0 (0 to 60.2)                  | 28.6 (20.9 to 37.3)            | 5.4 (0.7 to 18.2)                                  | 11.1 (3.1 to 26.1)                                  |

Notes:

[57] - TS

[58] - TS

[59] - TS

[60] - TS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Objective Response (According to RECIST v1.1)

|                 |   |
|-----------------|---|
| End point title | Duration of Objective Response (According to RECIST v1.1) |
|-----------------|---|

End point description:

Duration of objective response was measured from the time measurements criteria were met for CR/PR (whichever was first recorded) until the first date that recurrent or PD was objectively documented (taking as reference for PD the smallest measurements recorded since treatment started).

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

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

End point timeframe:

up to 116 weeks

| End point values                     | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|--------------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                   | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed          | 4 <sup>[61]</sup>              | 126 <sup>[62]</sup>            | 37 <sup>[63]</sup>                                 | 36 <sup>[64]</sup>                                  |
| Units: months                        |                                |                                |  |   |
| arithmetic mean (standard deviation) | 0 (± 0)                        | 9 (± 6.94)                     | 3.9 (± 0.07)                                       | 5.8 (± 2.36)  |

Notes:

[61] - TS

[62] - TS

[63] - TS

[64] - TS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Disease Control (According to RECIST v1.1)

|                 |  |
|-----------------|--|
| End point title | Duration of Disease Control (According to RECIST v1.1) |
|-----------------|--|

End point description:

Duration of disease control was defined as the time from the start of treatment to the time of progression or death (whichever occurred first), among patients with evidence SD, PR or CR.

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to

treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

|   |           |
|---|-----------|
| End point type                          | Secondary |
| End point timeframe:<br>up to 116 weeks |           |

| End point values                     | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|--------------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type                   | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed          | 4 <sup>[65]</sup>              | 126 <sup>[66]</sup>            | 37 <sup>[67]</sup>                                 | 36 <sup>[68]</sup>                                  |
| Units: months                        |                                |                                |  |   |
| arithmetic mean (standard deviation) | 7.4 (± 5.54)                   | 7.4 (± 5.45)                   | 4.9 (± 3.08)                                       | 5.9 (± 4.51)  |

Notes:

[65] - TS

[66] - TS

[67] - TS

[68] - TS

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-Free Survival (PFS) Time

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Progression-Free Survival (PFS) Time |
|-----------------|--------------------------------------|

End point description:

Progression-Free Survival was defined as the duration of time from start of treatment until the day of objective tumour progression confirmed by tumour imaging (PD according to RECIST 1.1) or death.

Treated set. 32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section

|   |           |
|---|-----------|
| End point type                          | Secondary |
| End point timeframe:<br>up to 116 weeks |           |

| End point values                 | Combination Arm - Afa40+Ctx250 | Combination Arm - Afa40+Ctx500 | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|----------------------------------|--------------------------------|--------------------------------|--|---|
| Subject group type               | Reporting group                | Reporting group                | Reporting group                                    | Reporting group                                     |
| Number of subjects analysed      | 4 <sup>[69]</sup>              | 126 <sup>[70]</sup>            | 37 <sup>[71]</sup>                                 | 36 <sup>[72]</sup>                                  |
| Units: months                    |                                |                                |  |   |
| median (confidence interval 95%) | 4.2 (1.4 to 13.8)              | 4.6 (4.2 to 6.3)               | 2.7 (1.1 to 3.7)                                   | 2.9 (1.8 to 4.8)                                    |

---

Notes:

[69] - TS

[70] - TS

[71] - TS

[72] - TS

---

### **Statistical analyses**

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 915 days

Adverse event reporting additional description:

32 patients in the Afa40-mono group had disease progression and were transitioned to treatment with Afa40+Ctx500. Thus the total of 203 patients (4+126+37+36) minus the 32 patients counted in both 'Afa-mono' and 'Afa40+Ctx500' treatments arms equals 171, the total number of patients started in participant flow section.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

### Reporting groups

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Combination Arm -Afa40+Ctx250 |
|-----------------------|-------------------------------|

Reporting group description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with Acquired Resistance (AR) to erlotinib or gefitinib)

Afatinib 40 mg + cetuximab 250 mg/m<sup>2</sup> (Afa40+Ctx250)

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Combination Arm - Afa40+Ctx500 |
|-----------------------|--------------------------------|

Reporting group description:

Combination Arm (includes the initial dose escalation and expansion cohort of upfront afatinib plus cetuximab in patients with AR to erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m<sup>2</sup> (Afa40+Ctx500)

|                       |  |
|-----------------------|--|
| Reporting group title | Sequential Arm - Afatinib Monotherapy (Afa40 Mono) |
|-----------------------|--|

Reporting group description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the Maximum Tolerated Dose (MTD) determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

Afatinib 40 mg (Afa40 Mono)

|                       |   |
|-----------------------|---|
| Reporting group title | Sequential Arm - Combination Therapy (Afa40+Ctx500) |
|-----------------------|---|

Reporting group description:

Sequential Arm (includes patients who received afatinib monotherapy and upon progression the combination of afatinib and cetuximab at the MTD determined in the combination arm. Patients still needed to have met the criteria for AR to erlotinib or gefitinib).

Afatinib 40 mg + cetuximab 500 mg/m<sup>2</sup> (Afa40+Ctx500)

| Serious adverse events                               | Combination Arm -<br>Afa40+Ctx250 | Combination Arm -<br>Afa40+Ctx500 | Sequential Arm -<br>Afatinib<br>Monotherapy (Afa40<br>Mono) |
|--|-----------------------------------|-----------------------------------|---|
| Total subjects affected by serious<br>adverse events |                                   |                                   |   |
| subjects affected / exposed                          | 3 / 4 (75.00%)                    | 63 / 126 (50.00%)                 | 12 / 37 (32.43%)  |
| number of deaths (all causes)                        | 0                                 | 38                                | 11  |
| number of deaths resulting from<br>adverse events    | 0                                 | 0                                 | 0   |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                |                 |                |
| Bladder cancer  |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0           | 0 / 0          |
| Malignant neoplasm progression                                      |                |                 |                |
| subjects affected / exposed   | 2 / 4 (50.00%) | 6 / 126 (4.76%) | 2 / 37 (5.41%) |
| occurrences causally related to treatment / all                     | 0 / 2          | 0 / 6           | 0 / 2          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 6           | 0 / 2          |
| Metastasis  |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 126 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0           | 0 / 0          |
| Neoplasm progression  |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0           | 0 / 0          |
| Vascular disorders  |                |                 |                |
| Deep vein thrombosis  |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0           | 0 / 0          |
| Embolism  |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 0 / 126 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0           | 0 / 0          |
| Hypotension   |                |                 |                |
| subjects affected / exposed   | 0 / 4 (0.00%)  | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all                     | 0 / 0          | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all                          | 0 / 0          | 0 / 0           | 0 / 0          |
| Surgical and medical procedures                                     |                |                 |                |
| Pain management   |                |                 |                |



|  |                |                 |                |
|--|----------------|-----------------|----------------|
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Surgery  |                |                 |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                |                 |                |
| Catheter site pain                                   |                |                 |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Chest pain   |                |                 |                |
| subjects affected / exposed                          | 1 / 4 (25.00%) | 1 / 126 (0.79%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Chills   |                |                 |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Death  |                |                 |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 2 / 126 (1.59%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 2           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 2           | 0 / 1          |
| Fatigue  |                |                 |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 3 / 126 (2.38%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 2 / 3           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| General physical health deterioration                |                |                 |                |
| subjects affected / exposed                          | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 1           | 0 / 0          |
| Mucosal inflammation                                 |                |                 |                |

|   |               |                 |                |
|---|---------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Oedema peripheral                               |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Pain  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Pyrexia   |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Sudden death                                    |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           | 0 / 0          |
| Immune system disorders                         |               |                 |                |
| Drug hypersensitivity                           |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 3 / 126 (2.38%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 3 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hypersensitivity                                |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Respiratory, thoracic and mediastinal disorders |               |                 |                |
| Acute respiratory distress syndrome             |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |

|   |               |                   |                |
|---|---------------|-------------------|----------------|
| Cough   |               |                   |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%)   | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1             | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0             | 0 / 0          |
| Dyspnoea  |               |                   |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 14 / 126 (11.11%) | 2 / 37 (5.41%) |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 16            | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 1 / 3             | 0 / 0          |
| Haemoptysis                                     |               |                   |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%)   | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1             | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1             | 0 / 0          |
| Hypoxia   |               |                   |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 4 / 126 (3.17%)   | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 5             | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 2             | 0 / 1          |
| Lung infiltration                               |               |                   |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%)   | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1             | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0             | 0 / 0          |
| Pleural effusion                                |               |                   |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 6 / 126 (4.76%)   | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 7             | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0             | 0 / 0          |
| Pneumonitis                                     |               |                   |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%)   | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 2             | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 1 / 1             | 0 / 0          |
| Pneumothorax                                    |               |                   |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%)   | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0             | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0             | 0 / 0          |
| Pulmonary embolism                              |               |                   |                |

|   |               |                 |                |
|---|---------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Pulmonary mass                                  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Respiratory failure                             |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Psychiatric disorders                           |               |                 |                |
| Confusional state                               |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           | 0 / 0          |
| Hallucination                                   |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Mental status changes                           |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Investigations                                  |               |                 |                |
| Biopsy lung                                     |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Injury, poisoning and procedural complications  |               |                 |                |
| Fall  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |

|   |               |                 |                |
|---|---------------|-----------------|----------------|
| Femur fracture                                  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hip fracture                                    |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Spinal compression fracture                     |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Spinal fracture                                 |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Cardiac disorders                               |               |                 |                |
| Atrial fibrillation                             |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Nervous system disorders                        |               |                 |                |
| Cerebrovascular accident                        |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Convulsion                                      |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 4 / 126 (3.17%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 5           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Depressed level of consciousness                |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           | 0 / 0          |

|   |               |                 |                |
|---|---------------|-----------------|----------------|
| Dizziness                                       |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Drug withdrawal headache                        |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Embolitic cerebral infarction                   |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Generalised tonic-clonic seizure                |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Headache  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Spinal cord compression                         |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Syncope   |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Blood and lymphatic system disorders            |               |                 |                |
| Leukocytosis                                    |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Eye disorders                                   |               |                 |                |

|   |               |                 |                |
|---|---------------|-----------------|----------------|
| Diplopia  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Gastrointestinal disorders                      |               |                 |                |
| Abdominal discomfort                            |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Abdominal distension                            |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 3           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Abdominal pain                                  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Ascites   |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Diarrhoea                                       |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 4 / 126 (3.17%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 4           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Dysphagia                                       |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Gastritis                                       |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Gastrointestinal haemorrhage                    |               |                 |                |

|   |               |                 |                |
|---|---------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Gastroesophageal reflux disease                 |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Nausea  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 4 / 126 (3.17%) | 2 / 37 (5.41%) |
| occurrences causally related to treatment / all | 0 / 0         | 4 / 6           | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Vomiting  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 6 / 126 (4.76%) | 3 / 37 (8.11%) |
| occurrences causally related to treatment / all | 0 / 0         | 3 / 7           | 2 / 3          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hepatobiliary disorders                         |               |                 |                |
| Hepatic failure                                 |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           | 0 / 0          |
| Hepatic function abnormal                       |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hyperbilirubinaemia                             |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Endocrine disorders                             |               |                 |                |
| Steroid withdrawal syndrome                     |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Musculoskeletal and connective tissue           |               |                 |                |



|   |                |                 |                |
|---|----------------|-----------------|----------------|
| disorders                                       |                |                 |                |
| Arthralgia                                      |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Back pain                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Bone pain                                       |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Musculoskeletal chest pain                      |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Musculoskeletal pain                            |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 2 / 126 (1.59%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Pain in extremity                               |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Spinal pain                                     |                |                 |                |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |
| Infections and infestations                     |                |                 |                |
| Cellulitis                                      |                |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |

|   |               |                 |                |
|---|---------------|-----------------|----------------|
| Cystitis  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Gastroenteritis                                 |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Gastroenteritis viral                           |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Infectious pleural effusion                     |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Meningitis aseptic                              |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Pneumonia                                       |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 3 / 126 (2.38%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 4           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Sepsis  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 1           | 0 / 0          |
| Streptococcal infection                         |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Urinary tract infection                         |               |                 |                |

|   |               |                 |                |
|---|---------------|-----------------|----------------|
| subjects affected / exposed                     | 0 / 4 (0.00%) | 2 / 126 (1.59%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 2           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Viral infection                                 |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Metabolism and nutrition disorders              |               |                 |                |
| Decreased appetite                              |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Dehydration                                     |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 5 / 126 (3.97%) | 2 / 37 (5.41%) |
| occurrences causally related to treatment / all | 0 / 0         | 2 / 5           | 1 / 2          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Failure to thrive                               |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hypercalcaemia                                  |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 1 / 37 (2.70%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hypokalaemia                                    |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 1 / 126 (0.79%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |
| Hyponatraemia                                   |               |                 |                |
| subjects affected / exposed                     | 0 / 4 (0.00%) | 0 / 126 (0.00%) | 0 / 37 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0           | 0 / 0          |

|                               |                  |  |  |
|-------------------------------|------------------|--|--|
| <b>Serious adverse events</b> | Sequential Arm - |  |  |
|-------------------------------|------------------|--|--|

|   | Combination<br>Therapy<br>(Afa40+Ctx500) |  |  |
|---|--|--|--|
| Total subjects affected by serious adverse events                   |  |  |  |
| subjects affected / exposed   | 15 / 36 (41.67%)                         |  |  |
| number of deaths (all causes)                                       | 13                                       |  |  |
| number of deaths resulting from adverse events                      | 0  |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |  |  |
| Bladder cancer  |  |  |  |
| subjects affected / exposed   | 0 / 36 (0.00%)                           |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                    |  |  |
| Malignant neoplasm progression                                      |  |  |  |
| subjects affected / exposed   | 4 / 36 (11.11%)                          |  |  |
| occurrences causally related to treatment / all                     | 0 / 4                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 4                                    |  |  |
| Metastasis  |  |  |  |
| subjects affected / exposed   | 0 / 36 (0.00%)                           |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                    |  |  |
| Neoplasm progression  |  |  |  |
| subjects affected / exposed   | 1 / 36 (2.78%)                           |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                    |  |  |
| Vascular disorders  |  |  |  |
| Deep vein thrombosis  |  |  |  |
| subjects affected / exposed   | 1 / 36 (2.78%)                           |  |  |
| occurrences causally related to treatment / all                     | 0 / 1                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                    |  |  |
| Embolism  |  |  |  |
| subjects affected / exposed   | 0 / 36 (0.00%)                           |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                                    |  |  |
| deaths causally related to treatment / all                          | 0 / 0                                    |  |  |
| Hypotension   |  |  |  |

|  |                |  |  |
|--|----------------|--|--|
| subjects affected / exposed                          | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Surgical and medical procedures                      |                |  |  |
| Pain management                                      |                |  |  |
| subjects affected / exposed                          | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Surgery  |                |  |  |
| subjects affected / exposed                          | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| General disorders and administration site conditions |                |  |  |
| Catheter site pain                                   |                |  |  |
| subjects affected / exposed                          | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Chest pain   |                |  |  |
| subjects affected / exposed                          | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Chills   |                |  |  |
| subjects affected / exposed                          | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all      | 1 / 1          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Death  |                |  |  |
| subjects affected / exposed                          | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |
| Fatigue  |                |  |  |
| subjects affected / exposed                          | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0          |  |  |
| deaths causally related to treatment / all           | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| General physical health deterioration           |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Mucosal inflammation                            |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Oedema peripheral                               |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pain  |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pyrexia   |                |  |  |
| subjects affected / exposed                     | 2 / 36 (5.56%) |  |  |
| occurrences causally related to treatment / all | 1 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sudden death                                    |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Immune system disorders                         |                |  |  |
| Drug hypersensitivity                           |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypersensitivity                                |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory, thoracic and mediastinal           |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| disorders                                       |                |  |  |  |
| Acute respiratory distress syndrome             |                |  |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Cough   |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Dyspnoea  |                |  |  |  |
| subjects affected / exposed                     | 2 / 36 (5.56%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Haemoptysis                                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Hypoxia   |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Lung infiltration                               |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pleural effusion                                |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumonitis                                     |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Pneumothorax                                    |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary mass                                  |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Respiratory failure                             |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 1          |  |  |
| Psychiatric disorders                           |                |  |  |
| Confusional state                               |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hallucination                                   |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Mental status changes                           |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Investigations                                  |                |  |  |
| Biopsy lung                                     |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Injury, poisoning and procedural                |                |  |  |



|   |                |  |  |
|---|----------------|--|--|
| complications                                   |                |  |  |
| Fall  |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Femur fracture                                  |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hip fracture                                    |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Spinal compression fracture                     |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Spinal fracture                                 |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cardiac disorders                               |                |  |  |
| Atrial fibrillation                             |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nervous system disorders                        |                |  |  |
| Cerebrovascular accident                        |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Convulsion                                      |                |  |  |

|   |                |  |  |  |
|---|----------------|--|--|--|
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Depressed level of consciousness                |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Dizziness                                       |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Drug withdrawal headache                        |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Embololic cerebral infarction                   |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Generalised tonic-clonic seizure                |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Headache  |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Spinal cord compression                         |                |  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Syncope   |                |  |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Blood and lymphatic system disorders            |                |  |  |
| Leukocytosis                                    |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Eye disorders                                   |                |  |  |
| Diplopia  |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal disorders                      |                |  |  |
| Abdominal discomfort                            |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal distension                            |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Abdominal pain                                  |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Ascites   |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Diarrhoea                                       |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Dysphagia                                       |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastritis                                       |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrointestinal haemorrhage                    |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastrooesophageal reflux disease                |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Nausea  |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Vomiting  |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatobiliary disorders                         |                |  |  |
| Hepatic failure                                 |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hepatic function abnormal                       |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyperbilirubinaemia                             |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Endocrine disorders                             |                |  |  |
| Steroid withdrawal syndrome                     |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal and connective tissue disorders |                |  |  |
| Arthralgia                                      |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Back pain                                       |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Bone pain                                       |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal chest pain                      |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Musculoskeletal pain                            |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pain in extremity                               |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|   |                |  |  |
|---|----------------|--|--|
| Spinal pain                                     |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Cellulitis                                      |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Cystitis  |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis                                 |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Gastroenteritis viral                           |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infectious pleural effusion                     |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Meningitis aseptic                              |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumonia                                       |                |  |  |
| subjects affected / exposed                     | 3 / 36 (8.33%) |  |  |
| occurrences causally related to treatment / all | 0 / 3          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Sepsis  |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Streptococcal infection                         |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Urinary tract infection                         |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Viral infection                                 |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Decreased appetite                              |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Dehydration                                     |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Failure to thrive                               |                |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypercalcaemia                                  |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hypokalaemia                                    |                |  |  |

|   |                |  |  |
|---|----------------|--|--|
| subjects affected / exposed                     | 0 / 36 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Hyponatraemia                                   |                |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

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

| Non-serious adverse events                            | Combination Arm -<br>Afa40+Ctx250 | Combination Arm -<br>Afa40+Ctx500 | Sequential Arm -<br>Afatinib<br>Monotherapy (Afa40<br>Mono) |
|---|-----------------------------------|-----------------------------------|---|
| Total subjects affected by non-serious adverse events |                                   |                                   |   |
| subjects affected / exposed                           | 4 / 4 (100.00%)                   | 126 / 126<br>(100.00%)            | 36 / 37 (97.30%)  |
| Vascular disorders                                    |                                   |                                   |   |
| Haematoma   |                                   |                                   |   |
| subjects affected / exposed                           | 1 / 4 (25.00%)                    | 1 / 126 (0.79%)                   | 0 / 37 (0.00%)  |
| occurrences (all)                                     | 1                                 | 1                                 | 0   |
| Haemorrhage   |                                   |                                   |   |
| subjects affected / exposed                           | 0 / 4 (0.00%)                     | 7 / 126 (5.56%)                   | 0 / 37 (0.00%)  |
| occurrences (all)                                     | 0                                 | 8                                 | 0   |
| Hot flush   |                                   |                                   |   |
| subjects affected / exposed                           | 1 / 4 (25.00%)                    | 0 / 126 (0.00%)                   | 0 / 37 (0.00%)  |
| occurrences (all)                                     | 1                                 | 0                                 | 0   |
| Intra-abdominal haematoma                             |                                   |                                   |   |
| subjects affected / exposed                           | 1 / 4 (25.00%)                    | 0 / 126 (0.00%)                   | 0 / 37 (0.00%)  |
| occurrences (all)                                     | 2                                 | 0                                 | 0   |
| General disorders and administration site conditions  |                                   |                                   |   |
| Asthenia  |                                   |                                   |   |
| subjects affected / exposed                           | 0 / 4 (0.00%)                     | 7 / 126 (5.56%)                   | 1 / 37 (2.70%)  |
| occurrences (all)                                     | 0                                 | 7                                 | 1   |
| Chest discomfort                                      |                                   |                                   |   |
| subjects affected / exposed                           | 0 / 4 (0.00%)                     | 4 / 126 (3.17%)                   | 0 / 37 (0.00%)  |
| occurrences (all)                                     | 0                                 | 4                                 | 0   |
| Chest pain  |                                   |                                   |   |



|  |                |                   |                  |
|--|----------------|-------------------|------------------|
| subjects affected / exposed              | 2 / 4 (50.00%) | 6 / 126 (4.76%)   | 1 / 37 (2.70%)   |
| occurrences (all)                        | 3              | 8                 | 1                |
| Chills                                   |                |                   |                  |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 14 / 126 (11.11%) | 2 / 37 (5.41%)   |
| occurrences (all)                        | 0              | 14                | 2                |
| Face oedema                              |                |                   |                  |
| subjects affected / exposed              | 1 / 4 (25.00%) | 0 / 126 (0.00%)   | 0 / 37 (0.00%)   |
| occurrences (all)                        | 1              | 0                 | 0                |
| Fatigue                                  |                |                   |                  |
| subjects affected / exposed              | 3 / 4 (75.00%) | 69 / 126 (54.76%) | 16 / 37 (43.24%) |
| occurrences (all)                        | 4              | 95                | 16               |
| Feeling cold                             |                |                   |                  |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 7 / 126 (5.56%)   | 1 / 37 (2.70%)   |
| occurrences (all)                        | 0              | 7                 | 1                |
| Mucosal inflammation                     |                |                   |                  |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 32 / 126 (25.40%) | 4 / 37 (10.81%)  |
| occurrences (all)                        | 0              | 58                | 5                |
| Oedema peripheral                        |                |                   |                  |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 12 / 126 (9.52%)  | 3 / 37 (8.11%)   |
| occurrences (all)                        | 0              | 12                | 4                |
| Pain                                     |                |                   |                  |
| subjects affected / exposed              | 1 / 4 (25.00%) | 14 / 126 (11.11%) | 1 / 37 (2.70%)   |
| occurrences (all)                        | 1              | 14                | 1                |
| Pyrexia                                  |                |                   |                  |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 21 / 126 (16.67%) | 8 / 37 (21.62%)  |
| occurrences (all)                        | 0              | 24                | 9                |
| Xerosis                                  |                |                   |                  |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 53 / 126 (42.06%) | 0 / 37 (0.00%)   |
| occurrences (all)                        | 0              | 85                | 0                |
| Immune system disorders                  |                |                   |                  |
| Drug hypersensitivity                    |                |                   |                  |
| subjects affected / exposed              | 0 / 4 (0.00%)  | 9 / 126 (7.14%)   | 0 / 37 (0.00%)   |
| occurrences (all)                        | 0              | 9                 | 0                |
| Reproductive system and breast disorders |                |                   |                  |

|   |                |                   |                  |
|---|----------------|-------------------|------------------|
| Pelvic pain                                     |                |                   |                  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 0 / 126 (0.00%)   | 2 / 37 (5.41%)   |
| occurrences (all)                               | 0              | 0                 | 2                |
| Respiratory, thoracic and mediastinal disorders |                |                   |                  |
| Cough   |                |                   |                  |
| subjects affected / exposed                     | 2 / 4 (50.00%) | 41 / 126 (32.54%) | 10 / 37 (27.03%) |
| occurrences (all)                               | 2              | 68                | 10               |
| Dysphonia                                       |                |                   |                  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 10 / 126 (7.94%)  | 3 / 37 (8.11%)   |
| occurrences (all)                               | 0              | 12                | 3                |
| Dyspnoea  |                |                   |                  |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 33 / 126 (26.19%) | 7 / 37 (18.92%)  |
| occurrences (all)                               | 1              | 45                | 7                |
| Epistaxis                                       |                |                   |                  |
| subjects affected / exposed                     | 2 / 4 (50.00%) | 25 / 126 (19.84%) | 5 / 37 (13.51%)  |
| occurrences (all)                               | 2              | 35                | 7                |
| Hiccups   |                |                   |                  |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 1 / 126 (0.79%)   | 0 / 37 (0.00%)   |
| occurrences (all)                               | 1              | 1                 | 0                |
| Hypoxia   |                |                   |                  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 2 / 126 (1.59%)   | 2 / 37 (5.41%)   |
| occurrences (all)                               | 0              | 2                 | 2                |
| Nasal congestion                                |                |                   |                  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 2 / 126 (1.59%)   | 2 / 37 (5.41%)   |
| occurrences (all)                               | 0              | 2                 | 3                |
| Nasal dryness                                   |                |                   |                  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 3 / 126 (2.38%)   | 3 / 37 (8.11%)   |
| occurrences (all)                               | 0              | 3                 | 3                |
| Oropharyngeal pain                              |                |                   |                  |
| subjects affected / exposed                     | 1 / 4 (25.00%) | 13 / 126 (10.32%) | 2 / 37 (5.41%)   |
| occurrences (all)                               | 1              | 13                | 2                |
| Pleural effusion                                |                |                   |                  |
| subjects affected / exposed                     | 0 / 4 (0.00%)  | 2 / 126 (1.59%)   | 2 / 37 (5.41%)   |
| occurrences (all)                               | 0              | 2                 | 2                |
| Pulmonary embolism                              |                |                   |                  |

|  |                     |                         |                        |
|--|---------------------|-------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 4 (0.00%)<br>0  | 2 / 126 (1.59%)<br>2    | 3 / 37 (8.11%)<br>3    |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 4 (0.00%)<br>0  | 15 / 126 (11.90%)<br>17 | 4 / 37 (10.81%)<br>4   |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)               | 0 / 4 (0.00%)<br>0  | 2 / 126 (1.59%)<br>2    | 0 / 37 (0.00%)<br>0    |
| Depression<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 4 (0.00%)<br>0  | 5 / 126 (3.97%)<br>5    | 2 / 37 (5.41%)<br>2    |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 4 (0.00%)<br>0  | 11 / 126 (8.73%)<br>11  | 5 / 37 (13.51%)<br>5   |
| Investigations<br>Haemoglobin decreased<br>subjects affected / exposed<br>occurrences (all)        | 0 / 4 (0.00%)<br>0  | 3 / 126 (2.38%)<br>3    | 0 / 37 (0.00%)<br>0    |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 4 (25.00%)<br>1 | 10 / 126 (7.94%)<br>10  | 5 / 37 (13.51%)<br>5   |
| Nervous system disorders<br>Cognitive disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0  | 1 / 126 (0.79%)<br>1    | 2 / 37 (5.41%)<br>2    |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 4 (0.00%)<br>0  | 17 / 126 (13.49%)<br>19 | 6 / 37 (16.22%)<br>6   |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 4 (0.00%)<br>0  | 10 / 126 (7.94%)<br>10  | 0 / 37 (0.00%)<br>0    |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                       | 1 / 4 (25.00%)<br>1 | 53 / 126 (42.06%)<br>68 | 10 / 37 (27.03%)<br>10 |
| Memory impairment  |                     |                         |                        |

|                                      |                |                   |                |
|--------------------------------------|----------------|-------------------|----------------|
| subjects affected / exposed          | 0 / 4 (0.00%)  | 1 / 126 (0.79%)   | 2 / 37 (5.41%) |
| occurrences (all)                    | 0              | 1                 | 2              |
| Neuropathy peripheral                |                |                   |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 11 / 126 (8.73%)  | 0 / 37 (0.00%) |
| occurrences (all)                    | 0              | 16                | 0              |
| Peripheral motor neuropathy          |                |                   |                |
| subjects affected / exposed          | 1 / 4 (25.00%) | 2 / 126 (1.59%)   | 0 / 37 (0.00%) |
| occurrences (all)                    | 1              | 2                 | 0              |
| Peripheral sensory neuropathy        |                |                   |                |
| subjects affected / exposed          | 1 / 4 (25.00%) | 7 / 126 (5.56%)   | 1 / 37 (2.70%) |
| occurrences (all)                    | 1              | 8                 | 1              |
| Blood and lymphatic system disorders |                |                   |                |
| Anaemia                              |                |                   |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 5 / 126 (3.97%)   | 2 / 37 (5.41%) |
| occurrences (all)                    | 0              | 5                 | 2              |
| Ear and labyrinth disorders          |                |                   |                |
| Ear pain                             |                |                   |                |
| subjects affected / exposed          | 1 / 4 (25.00%) | 2 / 126 (1.59%)   | 0 / 37 (0.00%) |
| occurrences (all)                    | 1              | 2                 | 0              |
| Ear pruritus                         |                |                   |                |
| subjects affected / exposed          | 1 / 4 (25.00%) | 1 / 126 (0.79%)   | 0 / 37 (0.00%) |
| occurrences (all)                    | 1              | 1                 | 0              |
| Eye disorders                        |                |                   |                |
| Dry eye                              |                |                   |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 13 / 126 (10.32%) | 2 / 37 (5.41%) |
| occurrences (all)                    | 0              | 15                | 2              |
| Eye irritation                       |                |                   |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 9 / 126 (7.14%)   | 1 / 37 (2.70%) |
| occurrences (all)                    | 0              | 10                | 1              |
| Lacrimation increased                |                |                   |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 9 / 126 (7.14%)   | 0 / 37 (0.00%) |
| occurrences (all)                    | 0              | 9                 | 0              |
| Vision blurred                       |                |                   |                |
| subjects affected / exposed          | 0 / 4 (0.00%)  | 8 / 126 (6.35%)   | 2 / 37 (5.41%) |
| occurrences (all)                    | 0              | 8                 | 2              |
| Gastrointestinal disorders           |                |                   |                |

|                              |                |                   |                  |
|------------------------------|----------------|-------------------|------------------|
| Abdominal pain               |                |                   |                  |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 10 / 126 (7.94%)  | 0 / 37 (0.00%)   |
| occurrences (all)            | 0              | 11                | 0                |
| Abdominal pain upper         |                |                   |                  |
| subjects affected / exposed  | 1 / 4 (25.00%) | 4 / 126 (3.17%)   | 0 / 37 (0.00%)   |
| occurrences (all)            | 1              | 4                 | 0                |
| Aphthous stomatitis          |                |                   |                  |
| subjects affected / exposed  | 1 / 4 (25.00%) | 2 / 126 (1.59%)   | 2 / 37 (5.41%)   |
| occurrences (all)            | 1              | 2                 | 2                |
| Cheilitis                    |                |                   |                  |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 13 / 126 (10.32%) | 3 / 37 (8.11%)   |
| occurrences (all)            | 0              | 15                | 3                |
| Constipation                 |                |                   |                  |
| subjects affected / exposed  | 1 / 4 (25.00%) | 32 / 126 (25.40%) | 3 / 37 (8.11%)   |
| occurrences (all)            | 1              | 46                | 3                |
| Diarrhoea                    |                |                   |                  |
| subjects affected / exposed  | 2 / 4 (50.00%) | 92 / 126 (73.02%) | 27 / 37 (72.97%) |
| occurrences (all)            | 3              | 244               | 34               |
| Dry mouth                    |                |                   |                  |
| subjects affected / exposed  | 1 / 4 (25.00%) | 14 / 126 (11.11%) | 0 / 37 (0.00%)   |
| occurrences (all)            | 1              | 14                | 0                |
| Glossodynia                  |                |                   |                  |
| subjects affected / exposed  | 1 / 4 (25.00%) | 5 / 126 (3.97%)   | 1 / 37 (2.70%)   |
| occurrences (all)            | 1              | 7                 | 1                |
| Haemorrhoids                 |                |                   |                  |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 4 / 126 (3.17%)   | 1 / 37 (2.70%)   |
| occurrences (all)            | 0              | 4                 | 1                |
| Large intestinal haemorrhage |                |                   |                  |
| subjects affected / exposed  | 1 / 4 (25.00%) | 0 / 126 (0.00%)   | 0 / 37 (0.00%)   |
| occurrences (all)            | 2              | 0                 | 0                |
| Lip dry                      |                |                   |                  |
| subjects affected / exposed  | 0 / 4 (0.00%)  | 1 / 126 (0.79%)   | 2 / 37 (5.41%)   |
| occurrences (all)            | 0              | 1                 | 2                |
| Nausea                       |                |                   |                  |
| subjects affected / exposed  | 3 / 4 (75.00%) | 64 / 126 (50.79%) | 11 / 37 (29.73%) |
| occurrences (all)            | 4              | 116               | 12               |

|  |                |                   |                 |
|--|----------------|-------------------|-----------------|
| Oral pain                              |                |                   |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 8 / 126 (6.35%)   | 0 / 37 (0.00%)  |
| occurrences (all)                      | 0              | 8                 | 0               |
| Stomatitis                             |                |                   |                 |
| subjects affected / exposed            | 1 / 4 (25.00%) | 16 / 126 (12.70%) | 4 / 37 (10.81%) |
| occurrences (all)                      | 1              | 23                | 4               |
| Tongue ulceration                      |                |                   |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 1 / 126 (0.79%)   | 0 / 37 (0.00%)  |
| occurrences (all)                      | 0              | 1                 | 0               |
| Vomiting                               |                |                   |                 |
| subjects affected / exposed            | 1 / 4 (25.00%) | 51 / 126 (40.48%) | 7 / 37 (18.92%) |
| occurrences (all)                      | 1              | 89                | 9               |
| Skin and subcutaneous tissue disorders |                |                   |                 |
| Alopecia                               |                |                   |                 |
| subjects affected / exposed            | 1 / 4 (25.00%) | 16 / 126 (12.70%) | 2 / 37 (5.41%)  |
| occurrences (all)                      | 1              | 16                | 2               |
| Dermatitis acneiform                   |                |                   |                 |
| subjects affected / exposed            | 1 / 4 (25.00%) | 22 / 126 (17.46%) | 7 / 37 (18.92%) |
| occurrences (all)                      | 1              | 30                | 8               |
| Dry skin                               |                |                   |                 |
| subjects affected / exposed            | 2 / 4 (50.00%) | 39 / 126 (30.95%) | 5 / 37 (13.51%) |
| occurrences (all)                      | 2              | 46                | 5               |
| Erythema                               |                |                   |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 14 / 126 (11.11%) | 0 / 37 (0.00%)  |
| occurrences (all)                      | 0              | 15                | 0               |
| Exfoliative rash                       |                |                   |                 |
| subjects affected / exposed            | 1 / 4 (25.00%) | 3 / 126 (2.38%)   | 1 / 37 (2.70%)  |
| occurrences (all)                      | 1              | 4                 | 1               |
| Hair growth abnormal                   |                |                   |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 3 / 126 (2.38%)   | 0 / 37 (0.00%)  |
| occurrences (all)                      | 0              | 3                 | 0               |
| Hirsutism                              |                |                   |                 |
| subjects affected / exposed            | 0 / 4 (0.00%)  | 17 / 126 (13.49%) | 0 / 37 (0.00%)  |
| occurrences (all)                      | 0              | 21                | 0               |
| Hyperhidrosis                          |                |                   |                 |

|                             |                |                    |                  |
|-----------------------------|----------------|--------------------|------------------|
| subjects affected / exposed | 1 / 4 (25.00%) | 1 / 126 (0.79%)    | 0 / 37 (0.00%)   |
| occurrences (all)           | 1              | 1                  | 0                |
| Pain of skin                |                |                    |                  |
| subjects affected / exposed | 0 / 4 (0.00%)  | 10 / 126 (7.94%)   | 0 / 37 (0.00%)   |
| occurrences (all)           | 0              | 11                 | 0                |
| Photosensitivity reaction   |                |                    |                  |
| subjects affected / exposed | 0 / 4 (0.00%)  | 8 / 126 (6.35%)    | 0 / 37 (0.00%)   |
| occurrences (all)           | 0              | 8                  | 0                |
| Pruritus                    |                |                    |                  |
| subjects affected / exposed | 1 / 4 (25.00%) | 50 / 126 (39.68%)  | 1 / 37 (2.70%)   |
| occurrences (all)           | 1              | 66                 | 1                |
| Rash                        |                |                    |                  |
| subjects affected / exposed | 1 / 4 (25.00%) | 106 / 126 (84.13%) | 14 / 37 (37.84%) |
| occurrences (all)           | 1              | 243                | 19               |
| Rash erythematous           |                |                    |                  |
| subjects affected / exposed | 2 / 4 (50.00%) | 2 / 126 (1.59%)    | 0 / 37 (0.00%)   |
| occurrences (all)           | 2              | 2                  | 0                |
| Rash macular                |                |                    |                  |
| subjects affected / exposed | 2 / 4 (50.00%) | 1 / 126 (0.79%)    | 0 / 37 (0.00%)   |
| occurrences (all)           | 2              | 1                  | 0                |
| Skin fissures               |                |                    |                  |
| subjects affected / exposed | 1 / 4 (25.00%) | 78 / 126 (61.90%)  | 5 / 37 (13.51%)  |
| occurrences (all)           | 1              | 130                | 5                |
| Skin hypertrophy            |                |                    |                  |
| subjects affected / exposed | 0 / 4 (0.00%)  | 2 / 126 (1.59%)    | 2 / 37 (5.41%)   |
| occurrences (all)           | 0              | 2                  | 2                |
| Skin irritation             |                |                    |                  |
| subjects affected / exposed | 0 / 4 (0.00%)  | 7 / 126 (5.56%)    | 0 / 37 (0.00%)   |
| occurrences (all)           | 0              | 7                  | 0                |
| Skin reaction               |                |                    |                  |
| subjects affected / exposed | 1 / 4 (25.00%) | 0 / 126 (0.00%)    | 0 / 37 (0.00%)   |
| occurrences (all)           | 1              | 0                  | 0                |
| Renal and urinary disorders |                |                    |                  |
| Dysuria                     |                |                    |                  |
| subjects affected / exposed | 1 / 4 (25.00%) | 9 / 126 (7.14%)    | 0 / 37 (0.00%)   |
| occurrences (all)           | 1              | 11                 | 0                |

|  |                     |                         |                       |
|--|---------------------|-------------------------|-----------------------|
| Haemoglobinuria<br>subjects affected / exposed<br>occurrences (all)      | 0 / 4 (0.00%)<br>0  | 1 / 126 (0.79%)<br>3    | 0 / 37 (0.00%)<br>0   |
| Musculoskeletal and connective tissue disorders                          |                     |                         |                       |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 4 (0.00%)<br>0  | 17 / 126 (13.49%)<br>20 | 1 / 37 (2.70%)<br>1   |
| Back pain<br>subjects affected / exposed<br>occurrences (all)            | 1 / 4 (25.00%)<br>3 | 27 / 126 (21.43%)<br>31 | 9 / 37 (24.32%)<br>10 |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)           | 0 / 4 (0.00%)<br>0  | 5 / 126 (3.97%)<br>7    | 2 / 37 (5.41%)<br>2   |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)        | 1 / 4 (25.00%)<br>1 | 14 / 126 (11.11%)<br>20 | 3 / 37 (8.11%)<br>3   |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all) | 1 / 4 (25.00%)<br>1 | 11 / 126 (8.73%)<br>11  | 2 / 37 (5.41%)<br>2   |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)              | 0 / 4 (0.00%)<br>0  | 12 / 126 (9.52%)<br>12  | 1 / 37 (2.70%)<br>1   |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)    | 1 / 4 (25.00%)<br>1 | 12 / 126 (9.52%)<br>13  | 1 / 37 (2.70%)<br>1   |
| Pain in jaw<br>subjects affected / exposed<br>occurrences (all)          | 1 / 4 (25.00%)<br>1 | 1 / 126 (0.79%)<br>1    | 0 / 37 (0.00%)<br>0   |
| Infections and infestations  |                     |                         |                       |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)           | 0 / 4 (0.00%)<br>0  | 2 / 126 (1.59%)<br>2    | 0 / 37 (0.00%)<br>0   |
| Candida infection<br>subjects affected / exposed<br>occurrences (all)    | 0 / 4 (0.00%)<br>0  | 3 / 126 (2.38%)<br>3    | 0 / 37 (0.00%)<br>0   |
| Eye infection  |                     |                         |                       |



|                                   |                |                   |                 |
|-----------------------------------|----------------|-------------------|-----------------|
| subjects affected / exposed       | 0 / 4 (0.00%)  | 4 / 126 (3.17%)   | 0 / 37 (0.00%)  |
| occurrences (all)                 | 0              | 4                 | 0               |
| Eyelid infection                  |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 1 / 126 (0.79%)   | 0 / 37 (0.00%)  |
| occurrences (all)                 | 0              | 1                 | 0               |
| Fungal infection                  |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 2 / 126 (1.59%)   | 0 / 37 (0.00%)  |
| occurrences (all)                 | 0              | 2                 | 0               |
| Impetigo                          |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 12 / 126 (9.52%)  | 0 / 37 (0.00%)  |
| occurrences (all)                 | 0              | 14                | 0               |
| Localised infection               |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 5 / 126 (3.97%)   | 0 / 37 (0.00%)  |
| occurrences (all)                 | 0              | 6                 | 0               |
| Nail infection                    |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 5 / 126 (3.97%)   | 2 / 37 (5.41%)  |
| occurrences (all)                 | 0              | 7                 | 2               |
| Nasopharyngitis                   |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 9 / 126 (7.14%)   | 1 / 37 (2.70%)  |
| occurrences (all)                 | 0              | 9                 | 1               |
| Paronychia                        |                |                   |                 |
| subjects affected / exposed       | 2 / 4 (50.00%) | 62 / 126 (49.21%) | 6 / 37 (16.22%) |
| occurrences (all)                 | 2              | 87                | 6               |
| Pneumonia                         |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 0 / 126 (0.00%)   | 2 / 37 (5.41%)  |
| occurrences (all)                 | 0              | 0                 | 2               |
| Rhinitis                          |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 6 / 126 (4.76%)   | 2 / 37 (5.41%)  |
| occurrences (all)                 | 0              | 6                 | 2               |
| Skin infection                    |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 6 / 126 (4.76%)   | 0 / 37 (0.00%)  |
| occurrences (all)                 | 0              | 8                 | 0               |
| Upper respiratory tract infection |                |                   |                 |
| subjects affected / exposed       | 0 / 4 (0.00%)  | 6 / 126 (4.76%)   | 3 / 37 (8.11%)  |
| occurrences (all)                 | 0              | 7                 | 3               |
| Urinary tract infection           |                |                   |                 |

|  |                    |                        |                      |
|--|--------------------|------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 4 (0.00%)<br>0 | 11 / 126 (8.73%)<br>14 | 5 / 37 (13.51%)<br>5 |
| Metabolism and nutrition disorders               |                    |                        |                      |
| Appetite disorder                                |                    |                        |                      |
| subjects affected / exposed                      | 1 / 4 (25.00%)     | 0 / 126 (0.00%)        | 0 / 37 (0.00%)       |
| occurrences (all)                                | 1                  | 0                      | 0                    |
| Decreased appetite                               |                    |                        |                      |
| subjects affected / exposed                      | 2 / 4 (50.00%)     | 28 / 126 (22.22%)      | 7 / 37 (18.92%)      |
| occurrences (all)                                | 3                  | 31                     | 7                    |
| Dehydration                                      |                    |                        |                      |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 2 / 126 (1.59%)        | 2 / 37 (5.41%)       |
| occurrences (all)                                | 0                  | 2                      | 2                    |
| Hypercalcaemia                                   |                    |                        |                      |
| subjects affected / exposed                      | 1 / 4 (25.00%)     | 1 / 126 (0.79%)        | 0 / 37 (0.00%)       |
| occurrences (all)                                | 3                  | 1                      | 0                    |
| Hyperglycaemia                                   |                    |                        |                      |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 3 / 126 (2.38%)        | 0 / 37 (0.00%)       |
| occurrences (all)                                | 0                  | 6                      | 0                    |
| Hypocalcaemia                                    |                    |                        |                      |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 9 / 126 (7.14%)        | 0 / 37 (0.00%)       |
| occurrences (all)                                | 0                  | 16                     | 0                    |
| Hypokalaemia                                     |                    |                        |                      |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 23 / 126 (18.25%)      | 3 / 37 (8.11%)       |
| occurrences (all)                                | 0                  | 33                     | 3                    |
| Hypomagnesaemia                                  |                    |                        |                      |
| subjects affected / exposed                      | 1 / 4 (25.00%)     | 37 / 126 (29.37%)      | 3 / 37 (8.11%)       |
| occurrences (all)                                | 2                  | 64                     | 3                    |
| Hyponatraemia                                    |                    |                        |                      |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 5 / 126 (3.97%)        | 2 / 37 (5.41%)       |
| occurrences (all)                                | 0                  | 5                      | 2                    |
| Hypophosphataemia                                |                    |                        |                      |
| subjects affected / exposed                      | 0 / 4 (0.00%)      | 0 / 126 (0.00%)        | 0 / 37 (0.00%)       |
| occurrences (all)                                | 0                  | 0                      | 0                    |

|                                   |  |  |  |
|-----------------------------------|--|--|--|
| <b>Non-serious adverse events</b> | Sequential Arm -<br>Combination<br>Therapy<br>(Afa40+Ctx500) |  |  |
|-----------------------------------|--|--|--|

|   |                   |  |  |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events |                   |  |  |
| subjects affected / exposed                           | 36 / 36 (100.00%) |  |  |
| Vascular disorders                                    |                   |  |  |
| Haematoma   |                   |  |  |
| subjects affected / exposed                           | 1 / 36 (2.78%)    |  |  |
| occurrences (all)                                     | 1                 |  |  |
| Haemorrhage   |                   |  |  |
| subjects affected / exposed                           | 0 / 36 (0.00%)    |  |  |
| occurrences (all)                                     | 0                 |  |  |
| Hot flush   |                   |  |  |
| subjects affected / exposed                           | 0 / 36 (0.00%)    |  |  |
| occurrences (all)                                     | 0                 |  |  |
| Intra-abdominal haematoma                             |                   |  |  |
| subjects affected / exposed                           | 0 / 36 (0.00%)    |  |  |
| occurrences (all)                                     | 0                 |  |  |
| General disorders and administration site conditions  |                   |  |  |
| Asthenia  |                   |  |  |
| subjects affected / exposed                           | 3 / 36 (8.33%)    |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Chest discomfort                                      |                   |  |  |
| subjects affected / exposed                           | 2 / 36 (5.56%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Chest pain  |                   |  |  |
| subjects affected / exposed                           | 2 / 36 (5.56%)    |  |  |
| occurrences (all)                                     | 2                 |  |  |
| Chills  |                   |  |  |
| subjects affected / exposed                           | 3 / 36 (8.33%)    |  |  |
| occurrences (all)                                     | 3                 |  |  |
| Face oedema   |                   |  |  |
| subjects affected / exposed                           | 0 / 36 (0.00%)    |  |  |
| occurrences (all)                                     | 0                 |  |  |
| Fatigue   |                   |  |  |
| subjects affected / exposed                           | 14 / 36 (38.89%)  |  |  |
| occurrences (all)                                     | 14                |  |  |
| Feeling cold  |                   |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| subjects affected / exposed                     | 2 / 36 (5.56%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Mucosal inflammation                            |                  |  |  |
| subjects affected / exposed                     | 2 / 36 (5.56%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Oedema peripheral                               |                  |  |  |
| subjects affected / exposed                     | 4 / 36 (11.11%)  |  |  |
| occurrences (all)                               | 5                |  |  |
| Pain  |                  |  |  |
| subjects affected / exposed                     | 4 / 36 (11.11%)  |  |  |
| occurrences (all)                               | 4                |  |  |
| Pyrexia   |                  |  |  |
| subjects affected / exposed                     | 6 / 36 (16.67%)  |  |  |
| occurrences (all)                               | 6                |  |  |
| Xerosis   |                  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| Immune system disorders                         |                  |  |  |
| Drug hypersensitivity                           |                  |  |  |
| subjects affected / exposed                     | 1 / 36 (2.78%)   |  |  |
| occurrences (all)                               | 1                |  |  |
| Reproductive system and breast disorders        |                  |  |  |
| Pelvic pain                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 36 (0.00%)   |  |  |
| occurrences (all)                               | 0                |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Cough   |                  |  |  |
| subjects affected / exposed                     | 11 / 36 (30.56%) |  |  |
| occurrences (all)                               | 11               |  |  |
| Dysphonia                                       |                  |  |  |
| subjects affected / exposed                     | 2 / 36 (5.56%)   |  |  |
| occurrences (all)                               | 2                |  |  |
| Dyspnoea  |                  |  |  |
| subjects affected / exposed                     | 7 / 36 (19.44%)  |  |  |
| occurrences (all)                               | 9                |  |  |
| Epistaxis                                       |                  |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Hiccups                     |                 |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Hypoxia                     |                 |  |  |
| subjects affected / exposed | 1 / 36 (2.78%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Nasal congestion            |                 |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Nasal dryness               |                 |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Oropharyngeal pain          |                 |  |  |
| subjects affected / exposed | 1 / 36 (2.78%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pleural effusion            |                 |  |  |
| subjects affected / exposed | 1 / 36 (2.78%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pulmonary embolism          |                 |  |  |
| subjects affected / exposed | 1 / 36 (2.78%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Rhinorrhoea                 |                 |  |  |
| subjects affected / exposed | 4 / 36 (11.11%) |  |  |
| occurrences (all)           | 4               |  |  |
| Psychiatric disorders       |                 |  |  |
| Anxiety                     |                 |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Depression                  |                 |  |  |
| subjects affected / exposed | 1 / 36 (2.78%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Insomnia                    |                 |  |  |
| subjects affected / exposed | 5 / 36 (13.89%) |  |  |
| occurrences (all)           | 5               |  |  |

|                                      |                  |  |  |
|--------------------------------------|------------------|--|--|
| Investigations                       |                  |  |  |
| Haemoglobin decreased                |                  |  |  |
| subjects affected / exposed          | 2 / 36 (5.56%)   |  |  |
| occurrences (all)                    | 4                |  |  |
| Weight decreased                     |                  |  |  |
| subjects affected / exposed          | 4 / 36 (11.11%)  |  |  |
| occurrences (all)                    | 4                |  |  |
| Nervous system disorders             |                  |  |  |
| Cognitive disorder                   |                  |  |  |
| subjects affected / exposed          | 1 / 36 (2.78%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Dizziness                            |                  |  |  |
| subjects affected / exposed          | 6 / 36 (16.67%)  |  |  |
| occurrences (all)                    | 8                |  |  |
| Dysgeusia                            |                  |  |  |
| subjects affected / exposed          | 2 / 36 (5.56%)   |  |  |
| occurrences (all)                    | 2                |  |  |
| Headache                             |                  |  |  |
| subjects affected / exposed          | 10 / 36 (27.78%) |  |  |
| occurrences (all)                    | 11               |  |  |
| Memory impairment                    |                  |  |  |
| subjects affected / exposed          | 1 / 36 (2.78%)   |  |  |
| occurrences (all)                    | 1                |  |  |
| Neuropathy peripheral                |                  |  |  |
| subjects affected / exposed          | 0 / 36 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Peripheral motor neuropathy          |                  |  |  |
| subjects affected / exposed          | 0 / 36 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Peripheral sensory neuropathy        |                  |  |  |
| subjects affected / exposed          | 0 / 36 (0.00%)   |  |  |
| occurrences (all)                    | 0                |  |  |
| Blood and lymphatic system disorders |                  |  |  |
| Anaemia                              |                  |  |  |
| subjects affected / exposed          | 3 / 36 (8.33%)   |  |  |
| occurrences (all)                    | 3                |  |  |
| Ear and labyrinth disorders          |                  |  |  |

|  |  |  |  |
|--|--|--|--|
| <p>Ear pain</p> <p>subjects affected / exposed</p> <p>1 / 36 (2.78%)</p> <p>occurrences (all)</p> <p>1</p> <p>Ear pruritus</p> <p>subjects affected / exposed</p> <p>0 / 36 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>  |  |  |  |
| <p>Eye disorders</p> <p>Dry eye</p> <p>subjects affected / exposed</p> <p>3 / 36 (8.33%)</p> <p>occurrences (all)</p> <p>3</p> <p>Eye irritation</p> <p>subjects affected / exposed</p> <p>1 / 36 (2.78%)</p> <p>occurrences (all)</p> <p>1</p> <p>Lacrimation increased</p> <p>subjects affected / exposed</p> <p>0 / 36 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Vision blurred</p> <p>subjects affected / exposed</p> <p>5 / 36 (13.89%)</p> <p>occurrences (all)</p> <p>5</p>  |  |  |  |
| <p>Gastrointestinal disorders</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>2 / 36 (5.56%)</p> <p>occurrences (all)</p> <p>2</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>1 / 36 (2.78%)</p> <p>occurrences (all)</p> <p>1</p> <p>Aphthous stomatitis</p> <p>subjects affected / exposed</p> <p>0 / 36 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Cheilitis</p> <p>subjects affected / exposed</p> <p>0 / 36 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>6 / 36 (16.67%)</p> <p>occurrences (all)</p> <p>7</p> <p>Diarrhoea</p> |  |  |  |

|  |                  |  |  |
|--|------------------|--|--|
| subjects affected / exposed            | 13 / 36 (36.11%) |  |  |
| occurrences (all)                      | 18               |  |  |
| Dry mouth                              |                  |  |  |
| subjects affected / exposed            | 4 / 36 (11.11%)  |  |  |
| occurrences (all)                      | 4                |  |  |
| Glossodynia                            |                  |  |  |
| subjects affected / exposed            | 2 / 36 (5.56%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Haemorrhoids                           |                  |  |  |
| subjects affected / exposed            | 2 / 36 (5.56%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Large intestinal haemorrhage           |                  |  |  |
| subjects affected / exposed            | 0 / 36 (0.00%)   |  |  |
| occurrences (all)                      | 0                |  |  |
| Lip dry                                |                  |  |  |
| subjects affected / exposed            | 1 / 36 (2.78%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Nausea                                 |                  |  |  |
| subjects affected / exposed            | 12 / 36 (33.33%) |  |  |
| occurrences (all)                      | 15               |  |  |
| Oral pain                              |                  |  |  |
| subjects affected / exposed            | 1 / 36 (2.78%)   |  |  |
| occurrences (all)                      | 1                |  |  |
| Stomatitis                             |                  |  |  |
| subjects affected / exposed            | 3 / 36 (8.33%)   |  |  |
| occurrences (all)                      | 3                |  |  |
| Tongue ulceration                      |                  |  |  |
| subjects affected / exposed            | 2 / 36 (5.56%)   |  |  |
| occurrences (all)                      | 2                |  |  |
| Vomiting                               |                  |  |  |
| subjects affected / exposed            | 6 / 36 (16.67%)  |  |  |
| occurrences (all)                      | 8                |  |  |
| Skin and subcutaneous tissue disorders |                  |  |  |
| Alopecia                               |                  |  |  |
| subjects affected / exposed            | 5 / 36 (13.89%)  |  |  |
| occurrences (all)                      | 5                |  |  |



|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| Dermatitis acneiform        |                  |  |  |
| subjects affected / exposed | 9 / 36 (25.00%)  |  |  |
| occurrences (all)           | 9                |  |  |
| Dry skin                    |                  |  |  |
| subjects affected / exposed | 13 / 36 (36.11%) |  |  |
| occurrences (all)           | 13               |  |  |
| Erythema                    |                  |  |  |
| subjects affected / exposed | 1 / 36 (2.78%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Exfoliative rash            |                  |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Hair growth abnormal        |                  |  |  |
| subjects affected / exposed | 3 / 36 (8.33%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Hirsutism                   |                  |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Hyperhidrosis               |                  |  |  |
| subjects affected / exposed | 1 / 36 (2.78%)   |  |  |
| occurrences (all)           | 1                |  |  |
| Pain of skin                |                  |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Photosensitivity reaction   |                  |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Pruritus                    |                  |  |  |
| subjects affected / exposed | 6 / 36 (16.67%)  |  |  |
| occurrences (all)           | 7                |  |  |
| Rash                        |                  |  |  |
| subjects affected / exposed | 17 / 36 (47.22%) |  |  |
| occurrences (all)           | 40               |  |  |
| Rash erythematous           |                  |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| Rash macular<br>subjects affected / exposed<br>occurrences (all)  | 0 / 36 (0.00%)<br>0    |  |  |
| Skin fissures<br>subjects affected / exposed<br>occurrences (all)   | 16 / 36 (44.44%)<br>17 |  |  |
| Skin hypertrophy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 36 (0.00%)<br>0    |  |  |
| Skin irritation<br>subjects affected / exposed<br>occurrences (all)   | 1 / 36 (2.78%)<br>1    |  |  |
| Skin reaction<br>subjects affected / exposed<br>occurrences (all)   | 0 / 36 (0.00%)<br>0    |  |  |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 36 (0.00%)<br>0    |  |  |
| Haemoglobinuria<br>subjects affected / exposed<br>occurrences (all)   | 2 / 36 (5.56%)<br>2    |  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 5 / 36 (13.89%)<br>6   |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 10 / 36 (27.78%)<br>10 |  |  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)  | 2 / 36 (5.56%)<br>2    |  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)   | 4 / 36 (11.11%)<br>4   |  |  |
| Musculoskeletal pain  |                        |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Myalgia                     |                 |  |  |
| subjects affected / exposed | 1 / 36 (2.78%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Pain in extremity           |                 |  |  |
| subjects affected / exposed | 3 / 36 (8.33%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Pain in jaw                 |                 |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Infections and infestations |                 |  |  |
| Bronchitis                  |                 |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 3               |  |  |
| Candida infection           |                 |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Eye infection               |                 |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Eyelid infection            |                 |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Fungal infection            |                 |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Impetigo                    |                 |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Localised infection         |                 |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)  |  |  |
| occurrences (all)           | 2               |  |  |
| Nail infection              |                 |  |  |
| subjects affected / exposed | 5 / 36 (13.89%) |  |  |
| occurrences (all)           | 5               |  |  |

|                                    |                  |  |  |
|------------------------------------|------------------|--|--|
| Nasopharyngitis                    |                  |  |  |
| subjects affected / exposed        | 1 / 36 (2.78%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Paronychia                         |                  |  |  |
| subjects affected / exposed        | 12 / 36 (33.33%) |  |  |
| occurrences (all)                  | 13               |  |  |
| Pneumonia                          |                  |  |  |
| subjects affected / exposed        | 0 / 36 (0.00%)   |  |  |
| occurrences (all)                  | 0                |  |  |
| Rhinitis                           |                  |  |  |
| subjects affected / exposed        | 1 / 36 (2.78%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Skin infection                     |                  |  |  |
| subjects affected / exposed        | 3 / 36 (8.33%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| Upper respiratory tract infection  |                  |  |  |
| subjects affected / exposed        | 3 / 36 (8.33%)   |  |  |
| occurrences (all)                  | 3                |  |  |
| Urinary tract infection            |                  |  |  |
| subjects affected / exposed        | 6 / 36 (16.67%)  |  |  |
| occurrences (all)                  | 6                |  |  |
| Metabolism and nutrition disorders |                  |  |  |
| Appetite disorder                  |                  |  |  |
| subjects affected / exposed        | 0 / 36 (0.00%)   |  |  |
| occurrences (all)                  | 0                |  |  |
| Decreased appetite                 |                  |  |  |
| subjects affected / exposed        | 8 / 36 (22.22%)  |  |  |
| occurrences (all)                  | 8                |  |  |
| Dehydration                        |                  |  |  |
| subjects affected / exposed        | 5 / 36 (13.89%)  |  |  |
| occurrences (all)                  | 5                |  |  |
| Hypercalcaemia                     |                  |  |  |
| subjects affected / exposed        | 1 / 36 (2.78%)   |  |  |
| occurrences (all)                  | 1                |  |  |
| Hyperglycaemia                     |                  |  |  |

|                             |                  |  |  |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 2 / 36 (5.56%)   |  |  |
| occurrences (all)           | 2                |  |  |
| Hypocalcaemia               |                  |  |  |
| subjects affected / exposed | 0 / 36 (0.00%)   |  |  |
| occurrences (all)           | 0                |  |  |
| Hypokalaemia                |                  |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Hypomagnesaemia             |                  |  |  |
| subjects affected / exposed | 11 / 36 (30.56%) |  |  |
| occurrences (all)           | 14               |  |  |
| Hyponatraemia               |                  |  |  |
| subjects affected / exposed | 3 / 36 (8.33%)   |  |  |
| occurrences (all)           | 3                |  |  |
| Hypophosphataemia           |                  |  |  |
| subjects affected / exposed | 2 / 36 (5.56%)   |  |  |
| occurrences (all)           | 2                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment  |
|-------------------|--|
| 11 June 2010      | <ul style="list-style-type: none"><li>• An exclusion criterion was added, whereby patients who required treatment with any prohibited medication were to be excluded from study participation. This change resulted from a Phase I study (1200.79) of the effects of ritonavir, a potent P-gp inhibitor, on the single-dose PK of 20 mg afatinib, a P-gp substrate, which indicated that, although the median t<sub>max</sub> and terminal half-life of afatinib were not affected, the rate and extent of afatinib absorption was increased by co-treatment with ritonavir.</li><li>• Potent P-gp inhibitors or inducers were identified and added to the list of prohibited medications based on results of Study 1200.79.</li></ul>   |
| 03 August 2010    | <ul style="list-style-type: none"><li>• The protocol was amended to:</li><li>• Extend the screening period, skip the unnecessary physical examination and safety laboratory tests at study entry, mandate the availability of safety laboratory test results prior to cetuximab infusion if clinically indicated, to clarify the CT scan field and the schedule, and to stress on a confirmation scan in case of response</li><li>• Broaden the tumour material used for EGFR mutation test</li><li>• Redefine DLT for hypomagnesaemia</li><li>• Specify the contraception duration</li><li>• Mandate the availability of safety laboratory test results when clinically indicated</li><li>• Clarify the administration of cetuximab</li><li>• Allow more flexibility in dose modification and management of AEs more</li><li>• Allow directing sequencing for EGFR mutation test</li></ul>  |
| 21 January 2011   | <p>The protocol was amended to:</p> <ul style="list-style-type: none"><li>• Increase the combination arm to better assess the safety as well as the preliminary anti-tumour activity of the combination therapy (afatinib and cetuximab) in EGFR T790M+ and EGFR T790M- NSCLC following the observation of confirmed objective responses in the currently enrolled patients.</li><li>• Clarify the timing of biopsy after development of acquired resistance, to include blood EGFR plasma DNA analysis and to clarify the PK sample requirement for the enlarged combination arm</li><li>• Shorten the erlotinib/gefitinib washout period during screening and reduce the surgery time restriction prior to study treatment</li><li>• Add plasma EGFR mutation analysis</li><li>• Modify the criterion for removal of patients from the study, patients with radiographic disease progression while achieving clinical benefit may remain on study and receive palliative therapy</li></ul>   |
| 14 September 2011 | <ul style="list-style-type: none"><li>• The protocol was amended to:</li><li>• Further evaluate safety and preliminary efficacy in patients with EGFR mutation positive NSCLC and acquired resistance to erlotinib/gefitinib.</li><li>• Evaluate safety and preliminary efficacy in patients with EGFR mutation positive NSCLC with acquired resistance to afatinib (BIBW 2992).</li><li>• Introduce Grade 2 intolerable rash and paronychia as dose reduction criteria; to revise dose modification scheme.</li><li>• Add progression-free survival, duration of disease control and duration of objective response as secondary endpoints.</li><li>• Add protocol clarifications as indicated (e.g. patients with hypersensitivity reaction to the drug may discontinue the causal drug only; patients with disease progression may continue either afatinib or both drugs if established benefit and no other preferable treatment options, DLT reporting time frame).</li><li>• Introduce optional rebiopsy and test serum EGFR mutation upon disease progression.</li></ul> |

|                  |   |
|------------------|---|
| 08 November 2012 | <ul style="list-style-type: none"> <li>• The protocol was amended to:</li> <li>• Modify the timing for the primary analysis to when the last patient in the combination arm had started treatment with afatinib plus cetuximab for 6 months, and when at least 80% of patients on the sequential arm had either withdrawn from the trial, progressed on the combination of afatinib plus cetuximab, or initiated afatinib and cetuximab combination therapy for at least 6 months.</li> </ul> |
|------------------|---|

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported